The New England
Journal of Medicine

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Volume 242 FEBRUARY 2, 1950 Number 5

ADVENTURES AMONG VIRUSES

I. Some Properties of Viruses*

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LONDON, ENGLAND

I HAVE first to express my appreciation of the honor of being asked to deliver the Edward K. Dunham lectures. I feel, of course, that the Lecture Committee probably invited me not so much because of any personal deserts of mine as because there is, in England, a Harvard hospital; and they doubtless considered it was right and proper for a representative from Harvard hospital in Salisbury to come and tell Harvard University what was going on "over there." As most of you know, the Harvard hospital was erected at Salisbury in Southern England in the dark days of the war; it was planned from this University and largely staffed from this University. At the end of the war it was given to the Ministry of Health, and since 1946 it has been the site of a Common Cold Research Unit and an Air Hygiene Unit run by the Medical Research Council and Ministry of Health. In my third lecture I propose to relate something of what we have been trying to do there, though I fear I shall not be able to report that the problem of the common cold has been solved.

As you know, many workers in the virus field undergo laboratory infections, which occur as an all too frequent retaliatory effort on the part of the viruses under study. My "adventures among viruses," however, will not recount hairbreadth escapes from these dangers; the title is merely a useful noncommittal one enabling me to talk of what I like in the field in which I have worked for a quarter of a century. My task is more difficult because Professor F. M. Burnet,[1] in the Dunham lectures of 1944, talked of "virus as an organism" and effectively covered the virus field in a manner I cannot hope to equal.

I propose to consider the properties of viruses from two quite different points of view, first as they equip it to be an efficient parasite and secondly as they bear on virus classification. Under the first heading I shall have to talk of the properties in relation to its environment; later I shall have to make a tentative approach to something rather more fundamental.

VIRUS AS PARASITE

To be a successful parasite, a virus needs three properties. It must be able to multiply in the host cell, and it must be able to get from one host to another. But life, for most viruses, is not all beer and skittles; there will come times when fresh juicy, susceptible hosts are not available. Many viruses need, therefore, a third thing — a mechanism, or mechanisms, for surviving in hard times, either as a persistent inhabitant of the host or in an intermediate host or elsewhere; I shall call this property "persistence" for short. The first property, ability to multiple profusely, could be called "fecundity." In virus diseases, the property runs closely parallel with "virulence," and it seems justifiable to use that word. All viruses, as intracellular parasites, presumably exist at the expense of the cell. One can look upon them as devouring the cell or as deviating the metabolism of the cell to make more virus instead of more cell. If this process is very vigorous, it will result in death of the cell and a brisk reaction of the host as a whole either to disintegrated cell products or to the virus itself, or both. Many viruses, perhaps most, normally exist as inapparent or latent infections. Their multiplication is, I imagine, slower, so that the cells attacked are not killed, or only so slowly that the host can replace them — the viruses are avirulent, or relatively so. In the country of Theobald Smith I do not need to emphasize that the perfect parasite is not the one that excites a violent reaction, produces disease and perhaps kills its host, but one in which host and parasite remain on good terms, with the parasite making adequate provision for the widespread distribution of its offspring.

The second property, that of power to spread from host to host, we may call "transmissibility" — or

*The first of the Edward K. Dunham lectures for the Promotion of the Medical Sciences, delivered at Harvard Medical School on November 3, 1949.

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mobility for short, remembering that we mean passive mobility and not motility. We could say "infectiousness," but that term is better applied to a disease than to a parasite since, besides the transmissibility of the parasite, the host's willingness to receive or lack of skill to repel the invader is involved. Transmissibility involves excretion from the host, in nasal or oral secretions, in milk or urine or feces or from the skin, or, alternatively, presence of virus in the blood in circumstances suitable for its transmission by a biting insect or other arthropod.

Persistence of Virus

This third property deserves more detailed attention, and we must consider persistence outside and inside the host. Outside, the virus may be very tough and resistant to physical insults. Influenza virus is known to survive in dust up to two weeks.[2] Smallpox can remain alive in dried-up crusts for over a year.[3] Rift Valley fever is known to be liable to infect those working with it. In a case recorded by Francis and Magill,[4] a subject caught the infection apparently from scraping and painting the walls of a room in which there had been mice infected with Rift Valley fever virus three months previously. All mice had been removed from the room at that time, and there seemed no other possibility of contact of the patient with the virus.

Another tough virus is that of malignant panleukopenia of cats, studied in Boston by Hammon and Enders[5] and known also as feline agranulocytosis and feline enteritis. Syverton and his colleagues[6] write of "the extraordinary spontaneous communicability of the infection by cage, room or body contact." In a limited experience I have met similar troubles, the disease having sometimes turned up in uninoculated controls and failed to do so in inoculated kittens. I need not blush on this account, for Hammon and Enders[5] write "all attempts up to the present time to devise satisfactory techniques for isolating the animals under the conditions available at Boston, where the disease is prevalent, have failed." There are also reports that in households where a cat has died of the disease, a new cat introduced months later soon becomes infected and dies likewise.

The transmission of the virus of foot-and-mouth disease that has dried on hay or other materials is a well known occurrence.

Most viruses, however, are less tough than those I have mentioned and are more apt to survive within an animal body. The animal may be an insect vector. There are many cases in which such a vector may remain infective throughout its life, but here more than passive persistence may be involved. There is evidence that the viruses of yellow fever and equine encephalomyelitis may actually multiply in mosquitoes. That of St. Louis encephalitis may be carried on transovarially in the bird mite *Dermanyssus gallinae*, just as scrub-typhus rickettsias can be in other mites. That is to say, eggs laid by an infected mite hatch out, the young nymphs are found to be still carrying the virus, and they, when they grow up, pass it on to yet another generation.[7] Shope[8] has produced evidence that swine-influenza virus may be carried in the ova of lung worms passed by an infected pig, and may survive for months while the hatched lung worms are passing a large part of their life-cycle within their intermediate host, the earthworm.

Of particular interest are the cases of virus persistence in the recovered vertebrate host. Indeed, one school of thought maintains that the enduring immunity that is a feature of many virus diseases can be attributed to the equally enduring persistence of virus in the host. It is true that many viruses can persist a long time, but there is no evidence that this is so whenever this life-long resistance is found. Psittacosis in birds is a good example of a virus disease in which infection is probably contracted in the nest, is commonly inapparent, persists indefinitely and may become apparent when some jolt upsets the host-parasite balance.[9] The virus may be excreted only or mainly when overt disease follows such a jolt. (You will find the jolt motif recurring in my discussions.) The jolt may be a sudden one but, in psittacosis, as shown by Meyer and Eddie,[10] may be a chronic one, owing to faulty management, particularly overcrowding.

The best example from human medicine is probably herpes simplex. Dodd, Johnston and Buddingh[11] showed that aphthous stomatitis in children is often due to the herpes virus. It is thus that many children doubtless become infected. Afterwards the virus seems to persist in the epidermal cells about the mouth as a latent infection. Different kinds of jolts seem effective in upsetting the balance in different people; fever induced by physical means or by infection, exposure to ultraviolet light, colds, menstruation and eating cheese are mentioned as being precipitating causes in different people. Chronic herpetic encephalitis in rabbits may pass to a latent state, and in this instance, sublethal anaphylactic shock is reported by Good and Campbell[12] as being a good jolting agent. In my third lecture I shall have occasion to discuss the effect of nonspecific stimuli of rather different types in precipitating a common cold, and the possibility that here, too, a jolt to a delicate equilibrium is concerned.

Herpes virus may cause an infection in childhood that persists through a person's life. So can psittacosis in nurseries of budgereegahs. But we can start earlier than that. The Bittner virus of mouse carcinoma — often called by the fainthearted the milk factor or agent — is transmitted from mother to suckling young in the first days of their lives, to remain latent forever unless changed

circumstances of a hormonal nature activate it. Earlier still is the latent infection with the virus of lymphocytic choriomeningitis, which Traub[13, 14] found in a colony of mice. Here infection apparently occurred regularly and invariably in utero; the mice then carried infection through their lives. Infection of stocks of mice latently infected with this virus may sometimes be revealed by the jolt of an intracerebral injection of sterile broth. The adaptation of the virus to Traub's mouse colony finally became so perfect that the mice were all immune, and virus could be demonstrated only by the injection of tissues into susceptible mice of another stock. To get earlier than this, one would have to suppose transmission of virus through the germ plasm. Even this may happen. I daresay some of you are not familiar with a disease of sheep common in Scotland — "scrapie"; it is so called because infected sheep itch most violently and rub their wool off against fences.[15] You may perhaps know it better by its English names of "goggles" or "rubbers" or by its other Scottish names "cuddy trot" and "yeuky pine." The disease is commonly fatal and is due to a subacute poliomyeloencephalitis; in the late stages there occur, besides itching, emaciation, inco-ordination, convulsions and coma. There has been much argument about the mode of transmission, but there are known to exist "scrapie rams"; these may be mated to ewes whose offspring will succumb to the disease, commonly at about the age of two years. The ewes themselves ordinarily remain well, and so may their offspring by another ram. The scrapie ram himself often goes down eventually. Transmission experiments were unsuccessful until it was found, somewhat accidentally, that the normal incubation period after inoculation was two years: earlier experimenters had not waited long enough. In this disease there is a strong suggestion that the disease is carried in, or in close association with, the sperm.

So, too, it is reported that an apparently normal cock from an infected flock may pass on fowl paralysis to his progeny.[16]

We have seen that an encephalitis virus may be transmitted hereditarily in bird mites. It is believed that the same transmissibility is true of some of the viruses pathogenic for insects. One remarkable example has come to my attention. There is a large black-white-and-orange moth in Europe, the garden tiger (*Arctia caja*); it is very variable and desirable to breed as a suitable subject for the study of genetics or (more often) for the production of fancy varieties for the collector's cabinet. Reports state that there is no difficulty in breeding in captivity for two or three generations but that, after that, virus infection is almost sure to appear and to afflict the larvae with a fatal flabbiness. It almost seems that in this case the unfavorable effects of raising the insects in captivity had a cumulative effect over several generations in tilting a balance in favor of a virus, transmitted through sperm or egg.

In all the diseases over which we have cast a roving eye, we must have seen that virulence, mobility and persistence are rarely all three high at the same time. An ambitious virus, vainly viewing itself as the dominant organism on the earth, might picture itself as possessing all these qualities in high degree — the ideal virus. Theobald Smith's ideal parasite would have its mobility and persistence high but its virulence low. In other viruses the state of affairs may change with changing environment or variation in the virus.

Such a virus as that of measles has high virulence and mobility but poor persistence; nevertheless, it manages to keep going, always finding some susceptible children even if it has to get carried to another area to do so. Herpes when causing stomatitis in infants is virulent and mobile, but does not persist long in its full glory. As the child grows to adult life it becomes for most of the time avirulent and not readily transferable but, such as it is, indefinitely persistent. So, too, psittacosis in the nest has persistence as its only long suit, until suitable conditions make it for a time virulent and mobile also. When man is infected the virus is highly virulent but hardly at all mobile or persistent. In only one of these diseases, measles, is the state of affairs fairly constant. In the others changing environmental conditions such as passage from one species to another may determine the state of affairs and in particular whether the virus will cause overt disease.

Variation in Viruses

Balance between parasite and host is rarely stable for long. Besides alterations in environment, we may have the equilibrium upset by variation and mutation on the part of the virus. This will have to be considered particularly in my second lecture in relation to influenza. Viruses and other small parasites multiply so rapidly compared with larger hosts that there is immense scope for rather rapid change and adaptation by selection of suitable variants. Indeed, a competition in the field of natural selection would give the viruses, in Burnet's[1] words, an "intolerable advantage" over their hosts if the latter had not been able to evolve an immunologic response to the threat.

Adaptive modification of a virus to existence in a new host is something familiar to all virus workers. Most of us virologists take advantage of it every day when we try to persuade some shy virus to grow in fertile eggs or in a small convenient laboratory animal.

Viruses and Cancer

Though it is a little apart from my main theme, I cannot refrain from commenting on some implications of the argument regarding the virus theory

of cancer. You may think this a little naughty of me, for I gather that in many quarters in this country it is considered not quite nice to mention viruses and cancer in the same breath. Indeed, I was rather expecting that I should be required to abjure not only communism and polygamy but also the virus theory of cancer before being allowed to land in this country. We have noted, in considering viruses of many kinds, how often a virus latently infects its host until a jolt to the virus-cell equilibrium brings about visible disease. We have seen how transmissibility of a virus, ability to infect other cells, is a varying property that may or may not be present. We have found that virus infection may begin in utero and possibly be transmitted even in the germ plasm. Finally, viruses are capable of great feats in the way of variation and adaptation, and they can also cause cell proliferation. We have, therefore, no grounds for maintaining that viruses cannot cause cancer because viruses do not have the qualities necessary to act the part. We need not find it difficult to believe in viruses that are almost ubiquitous, normally cause no visible disease, are transmitted in the earliest days of life and only in certain circumstances sustain a jolt that causes them to give rise to new growths. Bittner's[17] virus of mammary cancer in mice has all these properties. Perhaps it is straining my metaphor to speak of a jolt in this instance, for the hormonal influences that lead to induction of cancer may well operate by permitting selection of a mutant of the ordinary latent form of the virus to a form that is highly pathogenic but extremely labile.

There are reports of important recent findings from the laboratories of the Imperial Cancer Research Fund, in London, and I should like to give my views about these. Though I am sure none are present tonight, I sometimes suspect that there are pathologists who dislike the virus theory of cancer so heartily that they would bury their heads ostrich-like in the sand rather than risk seeing or hearing of it. From what I have seen of the recent work in London, I feel justified in urging that even the most intolerant ostrich ought to take his head for a short time out of the sand and give the work some attention.

I do not say that the ostrich in question should not exercise his critical judgment. There are published descriptions of new technical methods that should allow any careful worker to repeat the reported work, and I am confident there will be no difficulty in repeating the fundamental observations. These depend upon Dr. James Craigie's[18] attempts to introduce better quantitative methods into cancer research. In the course of this work he found that many mouse tumors could be preserved in suitable diluents in suspensions held at −76°C., and that one mouse sarcoma, $CH_3\beta$, could by an improved technic be completely dried and still retain its power to produce tumors. Subsequent experiments, at present of a purely qualitative nature, yield suggestive evidence that a number of other mouse cancers, sarcomas and carcinomas, will similarly retain their activity after being dried to a high degree of dryness. There is naturally a strong suspicion that transmission cannot be accounted for by the survival of an old intact cell and that something apart from the whole cancer cell is responsible, perhaps a virus. Naturally, some will leap directly to this conclusion, whereas others will be more cautious.

It is possible to argue that frozen cancer tissue could contain some living cells, and indeed we know that mammalian cells can survive freezing, but it is much harder to believe that complex mammalian cells in large numbers withstand intense desiccation. The histologic evidence is against it. The importance of the implications of this work is such that there is bound to be great controversy about whether all dried cells are necessarily dead. Fortunately, there should be no need to argue the point on the basis of preconceived ideas, for it should be possible to show in several ways whether or not cell transplantation can account for successful transmission with these materials. There is evidence on this point that is not yet published, but one method of approach will be obvious to all. A sarcoma virus would be expected to find a susceptible connective-tissue cell wherever it was introduced, whereas an epitheliotropic carcinoma virus should be effective only when placed in contact with appropriate epithelium. Grafted carcinoma cells, on the other hand, should not and do not have to be placed near epithelium. Clearly, then, if frozen or dried carcinoma tissue yields tumors wherever it is injected, it is likely to be acting by virtue of surviving cells; if it is effective only when placed in contact with suitable epithelium a virus or similar extrinsic agent may well be concerned. Epithelial tumors other than mammary ones should yield the best evidence; mammary tissue is so widespread in the subcutaneous tissues of the mouse that results are hard to interpret where breast cancers are concerned.

If the results show, as is reported, the presence of an active agent in mammary cancers of mice bearing the Bittner virus, the agent now described would necessarily have properties different from those of the Bittner virus as hitherto studied; it is much more labile and produces tumors in a matter of days or weeks, not months. Mutation to a more active but labile form seems likely. Rous,[19] on the basis of his work with cancers derived from Shope's[8] rabbit papilloma, deduced that the papilloma virus must undergo a mutation or succession of mutations before it gives rise to cancers. It seems possible that the question of mutation of latent cancer viruses will turn out to be a focal point in future studies of the cause of cancer.

I must, however, emphasize that what has so far been made known about the recent work does no more than bring the virus hypothesis once again into the foreground. How far it brings us will become manifest not through prejudice against it nor prejudice for it, but through more work, to acquire more facts. Fortunately, new ways are now suggested by which these facts may be extracted from reluctant nature.

Classification of Viruses

Physicochemical Properties

There has been some talk lately about the classification and nomenclature of viruses, and it is important to consider on what properties of viruses classification should be based. We have discussed their fitness as parasites in terms of three biologic properties, virulence, mobility and persistence, all of which are clearly quite unsuitable as a basis for classification, if only because of their variability. Some viruses attack insects, others birds, and others mammals, but this by itself is no good basis, for some, such as some encephalitis viruses, can live and probably multiply in arthropods, birds or mammals. Some viruses attack the central nervous system, and others abdominal viscera, but some, like yellow fever, are readily induced to change their tastes. Some viruses cause cell proliferation, and others cell necrosis. Many, however, cause cell proliferation at first and cell necrosis later. In one instance, that of Shope's[8] rabbit fibroma, two variants are known, one causing proliferative, and the other inflammatory lesions.[20] Some viruses are transmitted by arthropods, and others are not; others, such as that of lymphocytic choriomeningitis, may be transmitted by arthropods but more often travel otherwise.[21] In short, no purely biologic characters that we can see seem of much value as a basis for classification. We have to turn, then, to physicochemical and possibly biochemical criteria.

Sizes and shapes of viruses. Most species of virus seem more homogeneous in both size and shape than bacteria, though, as we shall see, methods used in their study may have tended to overemphasize this homogeneity. On the whole, viruses that seem to be related in other ways — the psittacosis group, the pox viruses and so on — seem to be in the same size range. The smaller viruses, perhaps because of technical difficulties, are only known yet as roughly round dots: I except the bacterial viruses with their organized heads and tails and the fibers of tobacco mosaic and some other plant viruses. Pock viruses such as vaccinia, however, have denser masses demonstrable within them by electron microscopy. Treatment of vaccinia with pepsin has shown that there are a dense center and a more translucent periphery, recalling the nucleus and cytoplasm of a higher organism — whether there is a true homology I should not like to say.[22] Psittacosis shows evidence of having a cell wall, as bacteria do. Some of the insect-pathogenic viruses are in the form of stout rods or of slender rods enveloped in a capsule-like mass.[23] A thread-like form for poliomyelitis-like viruses has been reported but is, I gather, not now accepted. Electron micrographs taken lately by my colleagues, Chu, Dawson and Elford,[24] have revealed unexpected filamentous forms in preparations of influenza and some related viruses.

The technics ordinarily used in the making of preparations for study with the electron microscope involve several cycles of differential centrifugation. These are quite effective, but by their very nature tend to sort out particles of rather uniform size. Chu, Dawson and Elford[24] took advantage of the adsorbability of influenza virus onto red blood cells of fowls. The cells were laked by saponin, and virus allowed to adsorb on the cell ghosts directly from infected allantoic fluids. Thus, all the virus, of whatever size or shape, was obtained. Preparations were fixed with osmic acid, and micrographs obtained either by direct transmission or by the technic of Williams and Wyckoff[25] of metallic shadowing. Recently isolated influenza virus A was found largely in the form of long filaments up to 10 μ long or 100 times as long as wide, but round bodies of the orthodox form were also present as well as bodies of intermediate forms. Strains passed many times in the laboratory were usually seen as single round or as double forms, only a little elongated. Some preparations show a beaded structure as if round forms were developing within the filaments, but the results are not consistent with the view that the filaments are formed by subsequent end-to-end aggregation of previously separate round forms. A few filamentous forms of influenza virus were figured by Mosley and Wyckoff,[26] but their importance was overlooked. Heinmets and Golub[27] also described such forms but attributed them to degenerative changes. Chu, Dawson and Elford[24] found them present in fresh material, not increasing on storage, and unaffected by collagenase (this is important in proving that they are not collagen fibers). Their adsorption and elution from red cells parallel those of round forms of virus. They can be seen by ordinary dark-ground illumination, and this technic allows us to see directly their agglutination by homologous antiserums. In short, all evidence yet available indicates that they represent a form of influenza virus itself; what this can mean in terms of a possible life cycle of the virus we do not yet know. Similar pictures can be obtained with fowl-plague virus. The stringy forms seen in preparations of virus from Newcastle disease of fowls are probably of different nature. From several quarters there are suggestions that early in the multiplication of bacterial and other viruses, a stage

may be passed in which the virus is in an incomplete form, capable of being built up into complete virus but until then not demonstrable as an infectious agent. The facts adduced are difficult to interpret, and it is wise to suspend judgment for the time being.

Hirst's finding that preparations of influenza virus will agglutinate fowl red cells has opened up an enormous field. The discovery that the viruses of fowl plague, Newcastle disease and mumps have similar properties suggests that these form a closely related group. Their adsorption on and reaction with the surface of the red-cell membrane are almost certainly due to activity of an enzyme; there is thus, here, the beginning of a biochemical basis for sorting out these viruses.

Andrewes and Horstmann[28] studied the resistance of some 25 viruses to treatment with ethyl ether, and evidence concerning 10 other viruses was available from the literature. Viruses seemed all to be highly sensitive or highly resistant; in the latter group were the poxes, the bacterial viruses and the very smallest animal viruses — and also those of rabies and rabbit papilloma. The others studied were all sensitive. Consideration of size along with ether sensitivity enabled us to place the viruses studied in rough groups; those in these groups showed also many biologic properties in common. Such a grouping is only helpful in a very preliminary way to a taxonomic approach to the viruses.

Many other biochemical criteria, such as their content in different nucleic acids, can be applied to the classification of viruses. All these are lines of study upon which we are just entering, and progress is likely to be slow and sure but ultimately very great. But we are, I repeat, only feeling our way toward finding out what criteria can best be used. It caused therefore some disquiet to most sober virologists in Europe, and I find in America also, when the latest edition of Bergey's *Manual of Determinative Bacteriology* propounded an elaborate classification of plant, bacterial and animal viruses, complete with a binomial nomenclature according to Linnaeus. I believe that such a binominal nomenclature will come in time, but we are not ready for it for many years yet and I cannot imagine that many will use this particular system. Nor can I believe that a classification made when we have not decided on what basis to classify can be valid. It is, however, likely that an attempt may be made to apply the laws of priority to names created in what corresponds essentially, as regards viruses, to a pre-Linnaean epoch. If the time is not yet ripe for a formal classification of viruses, it is within the competence of an international microbiologic congress and its nomenclature commission to admit that fact and to lay down that no names shall be valid before a day in the future to be decided by that body in consultation with virologists. Zoologists, botanists and others at present squabble endlessly over dubious names dug up from the past. Virologists have never used binomials as yet, and would gain all and lose nothing by "starting fair"; they can place themselves in a sounder position than all other taxonomists by appropriate action before it is too late. They have, however, the difficult task of convincing others that bold action is not necessarily wicked.

My adventuring among viruses this afternoon has led me into many parts of the field, in the endeavor to lay hold of some general principles of value. In my next two lectures I propose to concentrate on a more limited field and to deal with influenza and the common cold. My hope is that the general principles considered today may help in the understanding of those two very troublesome afflictions.

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SOME OBSERVATIONS ON THE NATURAL BEHAVIOR OF CANCER IN MAN*

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IT IS generally accepted by surgeons that cancer grows in a steady and irrevocable manner, the rate of which is a function of the particular tumor and bears a fairly close relation to the histologic appearance of the lesion. Not only are apparent arrests or regressions of tumors usually attributed to faulty observations or recent therapy but also little or no consideration is given to the possibility of a natural resistance to cancer. The thesis of this paper is that malignant neoplasms undergo periods of spontaneous arrest or regression alternating with periods of growth and that this phenomenon is a function, at least in part, of local tissue resistance. Although the evidence is largely circumstantial,

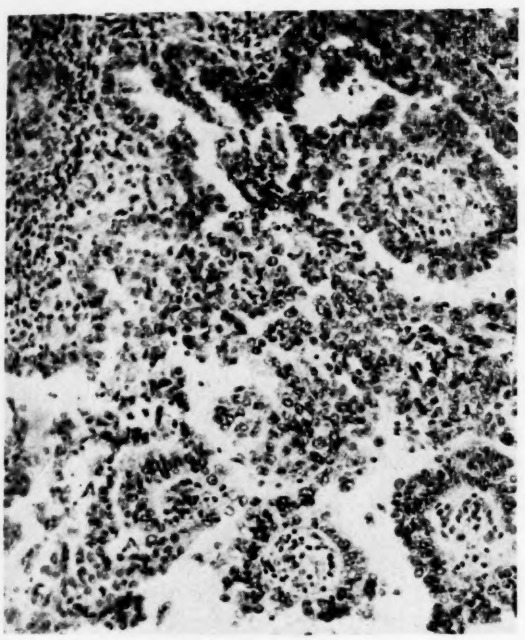

Figure 1. *Photomicrograph of Original Pelvic Tumor, Showing It to Be a Small-Cell Papillary Tumor of Moderately Rapid Growth (x100).*

this view, as a working hypothesis, has practical applications in the treatment of cancer and in the evaluation of methods of therapy.

Spontaneous Regression of Cancer‡

Case 1. A 54-year-old woman entered the hospital on October 1, 1936, complaining of lower abdominal pain. The present illness was of 6 weeks' duration. It was characterized by crampy intermittent pain in the right lower quadrant of the abdomen, frequency of urination and, in the 3 weeks prior to admission, increasing constipation. There had been a loss of weight of 6 pounds during the present illness. Three years previously a perineal repair and a suspension of the uterus had been performed at another hospital. The patient had had six normal pregnancies prior to her menopause, which had occurred 7 years before admission.

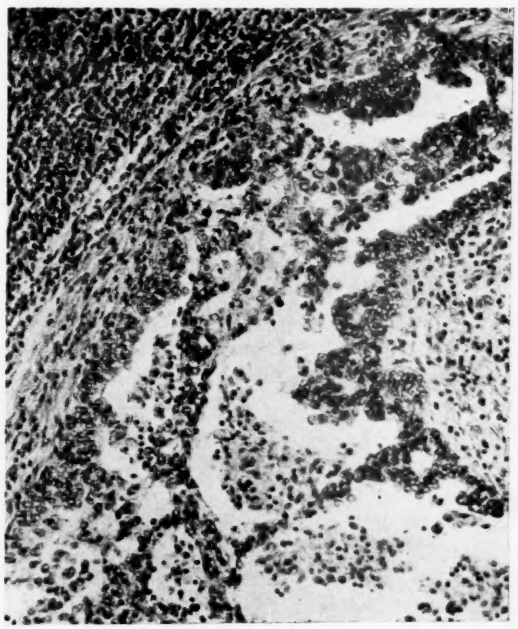

Figure 2. *Photomicrograph of Metastatic Lesion in Groin, Which Appeared After Spontaneous Regression of the Pelvic Neoplasm (x100). (Note the Similarity to the Original Biopsy.)*

Physical examination disclosed no abnormalities except for a large ventral hernia and a hard, nontender mass palpable in the pouch of Douglas. The uterus and the mass were in continuity and both were immovable.

The red-cell count, hemoglobin and white-cell count were normal. Examination of the urine was negative.

A gastrointestinal series and a barium enema revealed no abnormality.

On October 3 exploratory laparotomy disclosed a hard, nodular mass in the pelvis consistent with carcinomatosis. Many loops of small bowel were fixed to a solid tumor in the hollow of the sacrum. The right ovary was normal, but the adnexa and the posterior aspect of the uterus were incorporated in the mass. Palpation of the abdomen revealed similar nodules scattered throughout the omentum. No metastases were felt in the liver. A biopsy showed the tumor to be a small-cell carcinoma (Fig. 1). Extirpation of the lesion was considered to be impossible. The ventral hernia was repaired as the wound was closed. The postoperative course was uneventful.

During the next 2 years, the patient had intermittent attacks of abdominal pain, and in October, 1938, arrangements were made for terminal care at home. However, about this time she began to improve, and as she continued to enjoy good health she did not return to the hospital for 7 years.

*Presented at the annual meeting of the New England Surgical Society, Bretton Woods, New Hampshire, September 24, 1949.

†Assistant professor of surgery, Harvard Medical School; surgeon, Peter Bent Brigham Hospital.

‡The adjective "spontaneous" is used only in the sense that regression of growth ensued without the benefits of radiation, or surgical or hormonal therapy.

The patient re-entered the hospital in February, 1946, complaining of a mass in the right groin of 1 year's duration. There had been progressive, painless enlargement of the mass since it first appeared. Physical examination revealed a woman in good general health. There was a firm, smooth, fixed mass in the right groin. It measured approximately 8 by 4 by 4 cm. in size and was consistent with an incarcerated inguinal hernia. Abdominal and pelvic examinations were negative. The original tumor mass in the pelvis had entirely disappeared. The uterus was now freely movable and quite normal to palpation.

X-ray examination of the chest revealed diffuse nodular markings throughout both lungs consistent with miliary metastases. Films of the skull, spine and long bones showed no evidence of metastases.

Examination of the blood disclosed a hemoglobin of 12.6 gm. and a white-cell count of 7000. The urine was normal. The alkaline phosphatase was 2.1 Bodansky units.

The lesion in the right groin was explored and found to be a well encapsulated mass of neoplastic lymph nodes. A clean excision was easily accomplished. Histologic examination of the specimen revealed a mass of lymph nodes heavily infiltrated with a rapidly growing carcinoma. The structure of the tumor was similar to that of the original lesion. The cells were of the same type, but there was now a papillary arrangement of the tumor not seen in the original biopsy (Fig. 2). It was the opinion of the pathologist that the mass in the groin represented a metastasis of the original tumor.

In the course of the next year and a half the patient lost 20 pounds in weight. There was no evidence of recurrence of the tumor, however, and x-ray films of the chest showed no progression of the nodular markings. At this time she was found to have mild diabetes mellitus, and after regulation her weight was stabilized.

In May, 1948, she re-entered the hospital because of a small lump in the right side of the neck. This had developed in the course of the preceding year. Physical examination disclosed a soft nodule in the region of the superior pole of the right lobe of the thyroid gland. There was a recurrence of the ventral hernia, which made palpation of the abdomen and pelvis quite easy. No abnormalities could be detected. The remainder of the examination was negative.

Laboratory studies were within normal limits.

X-ray films of the chest revealed no change. In view of this the fine miliary markings were interpreted as fibrosis rather than neoplasm.

At operation the nodule in the neck proved to be a benign lipoma.

At the present time, 13 years after the original inoperable pelvic tumor was discovered and nearly 4 years since excision of the metastasis in the groin, the patient is alive and well and apparently free of active neoplasm. The course of this tumor is shown in Figure 3.

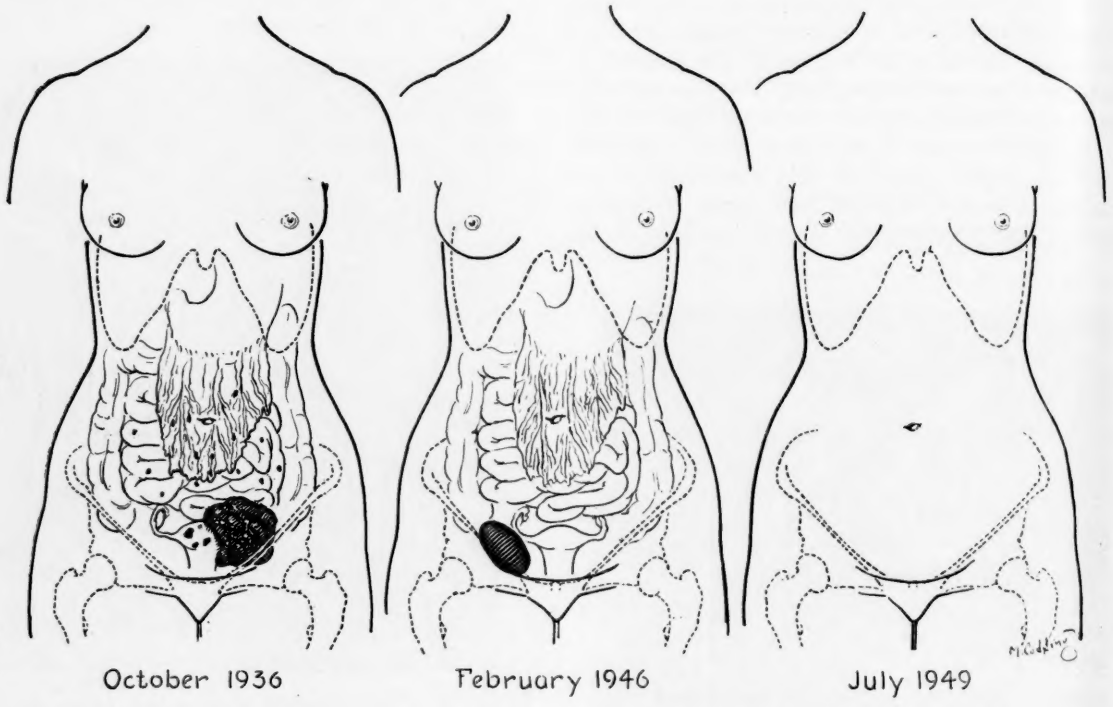

FIGURE 3. *Diagrammatic Representation of the Extent and Regression of a Small-Cell Pelvic Carcinoma (Case 1). The lesion in the groin was excised surgically.*

This case is reported to demonstrate that cancer may regress spontaneously. Although this is not the usual course of neoplastic disease, it is probably more common than has been realized. The older literature contains many accounts of spontaneous cures, but adequate histologic confirmation of the diagnosis is lacking.[1] Recently, McSwain et al.[2] described a case of Ewing's sarcoma in which pulmonary metastases apparently disappeared. Davis[3] has recorded 2 cases in which carcinoma of the bladder regressed after ureterosigmoidostomy, and similar regressions have been observed at the Peter Bent Brigham Hospital by Dr. J. H. Harrison.[4]

The occurrence of spontaneous regressions renders untenable the hypothesis that "cancer is a progressive, lawless, autonomous growth dependent upon the host only for its blood supply." It implies that

some of the many factors, exogenous and endogenous, that may lead to neoplasia in the first place are essential for progression of the lesion. The alteration or withdrawal of these factors, even in advanced stages of the disease, can result in dissolution of the tumor. This concept, if correct, is of the utmost importance because it allows for a natural resistance to neoplasia on the part of the organism and implies that the total destruction of every cancer cell is not necessarily essential for five-year or ten-year arrests.

Prolonged Arrest or Quiescence of Cancer

A natural resistance to the spread of cancer was postulated by many of the older pathologists. Round-cell infiltration and fibrosis in certain tumors lend support to this view. Experimental studies of tumor transplants provide considerable evidence for active resistance on the part of the host. Here, again, the predominance of lymphocytic and round-cell infiltration led Ewing[5] to conclude that "the lymphocyte is an important agent of defense against tumor growth."

The clinical evidence for a natural resistance against cancer is only circumstantial. However, it can be inferred from the development of late recurrences, the regression or arrest of tumor in one site while it is progressing elsewhere, and the occasional explosive spread of cancer. The following cases are illustrative.

Case 2. A 69-year-old unmarried woman entered the hospital in July, 1947, because of cholelithiasis. She had had vague indigestion and intolerance to fatty foods for many years, and in the year preceding admission had had two episodes of severe biliary colic. She had lost 20 pounds in weight in the last year, which she attributed to the fact that she had been eating very little for fear of inducing an attack of biliary pain. The past history was significant in that she had had a radical mastectomy for cancer of the right breast at another hospital 14 years before. She had enjoyed excellent health until the onset of the present illness.

Physical examination revealed a frail but well preserved woman. The scar of the right breast was thickened but showed no evidence of local recurrence. The general physical examination was negative, as was examination of the urine.

The red-cell count, white-cell count and hemoglobin determination were within normal limits.

An x-ray film of the gall bladder was interpreted as showing poor function and calculi.

On July 16 cholecystectomy and an incidental appendectomy were performed. Pathological studies of the gall bladder disclosed many calculi and a chronically fibrosed organ. However, at that time the Department of Pathology was carrying out serial sections of normal appendixes in a search for carcinoid tumors. Thus, it came about that a section through the tip of the appendix showed a group of irregular acini, the cells of which varied greatly in size and shape and were undergoing slight mitotic activity. A diagnosis of metastatic carcinoma of the appendix was made. Histologically, the cells were consistent with a breast cancer (Fig. 4).

The postoperative course was uneventful until the 14th day when pain in the right side of the chest, accompanied by a pleural effusion, developed. The chest was tapped, and 1100 cc. of serosanguineous fluid obtained. A cell block revealed tumor cells.

No further treatment was advised until the natural course of the tumor could be observed. Nine months later, in April, 1948, the chest tap was repeated. A cell block revealed atypical cells consistent with tumor cells. Meanwhile the patient felt well, maintained her weight and was moderately active. One year later, chest tap was again performed. On this occasion no tumor cells could be found in the fluid. A Papanicolaou smear also failed to disclose tumor cells.

Two years after metastatic cancer was demonstrable the patient's condition was essentially unchanged. She was active, ate well and maintained her weight. There was a moderate amount of fluid in the right side of the chest, but not enough to cause dyspnea at rest. No evidence of further metastases could be found on physical or x-ray examination.

In the last few months the patient has been given small doses of estrogens by her physician, and there is now questionable evidence of further slow progression of the pleural lesion.

Figure 4. *Photomicrograph of Tumor Cells in the Appendix Consistent with Metastatic Cancer of the Breast (x100).*

This case provides concrete evidence of the generally accepted theory that metastatic lesions may remain dormant for years. The local recurrence of cancer in a scar many years after the original operation is a well accepted observation and provides additional evidence that seeded cancer may be held in check for long periods, presumably by some, as yet unknown, biologic factors. In the case reported above there is evidence that cells with all the histologic criteria for malignant degeneration have been inactive for at least two years and probably ever since the original mastectomy sixteen years earlier.

The rapid growth of metastatic cancer at one site while it remains dormant elsewhere is another example of natural resistance to cancer that leads one to postulate that the mechanism of resistance is, at least in part, dependent upon local tissue metabolism.

CASE 3. A 55-year-old mother of 2 children entered the hospital on November 31, 1946, because of chronic partial obstruction of the large intestine. She had enjoyed excellent health until the present illness.

Physical examination disclosed moderate distention of the abdomen. The edge of the liver was palpable. No other abnormalities were noted.

Laboratory studies were noncontributory.

A barium enema revealed a partially obstructing neoplasm of the splenic flexure of the colon.

After adequate preparation, laparotomy was performed. At exploration the splenic flexure was the site of a large but easily resectable tumor. There were several obvious metastases in the liver, but no other metastases were found. The ovaries were small and atrophic. The tumor was resected, and an end-to-end anastomosis of the colon performed. Convalescence was uneventful. One year later the patient was in excellent health. Examination of the abdomen was negative.

Eighteen months after the original operation, the patient re-entered the hospital because of vaginal bleeding, abdominal pain and intermittent constipation and diarrhea. Examination now revealed the liver to be slightly enlarged and nodular, and there was a mass filling the pelvis that was believed to be consistent with a large ovarian tumor.

Operation was performed, and a partially cystic adenocarcinoma of the left ovary was removed. It measured 12 cm. in diameter. The opposite ovary was excised. Examination of the liver revealed many nodules scattered throughout the organ, but the general size of the liver was not greatly different from that at the previous operation.

Convalescence was satisfactory, and the patient, although easily fatigued, remained in good general health until December, 1948. From then until her death in March, 1949, she ran a slowly downhill course, with progressive enlargement of the liver, loss of weight and cachexia.

In this case established secondary cancer of the liver progressed so slowly that the patient remained well and active for nearly two years. Yet metastatic cancer of the ovary, which could not be detected by palpation at the time of the original operation, grew to a size of 12 cm., presumably in less than six months. Many such cases of the bizarre behavior of metastatic cancer could be cited. It may be significant that tumors that characteristically metastasize by way of the blood stream are particularly apt to behave in this fashion. For example, hypernephromas and thyroid cancer not infrequently result in large solitary metastatic lesions while the original growth remains so small as to be unrecognizable. The rarity of metastatic lesions in the spleen, despite the fact that this organ is a common site for infarction, implies that tumor cells find it an unfavorable medium for growth. Such facts as the foregoing led the older pathologists to talk of the necessity for a prepared soil for successful tumor metastasis and conversely may be interpreted as evidence of local tissue resistance.

Finally, the explosive spread of certain cancers after long periods of slow progression or even quiescence may be interpreted as a sudden breakdown of the defenses of the host. This not infrequently follows surgical procedures and is usually ascribed to incomplete excision with seeding of tumor cells into blood vessels and lymphatics. The actual mechanism is probably much more complex because the converse of this is also seen after surgical procedures — namely, the long arrest of cancer after palliative resection.

In the following case it appears that surgical intervention led to a breakdown between the resistance of the host and the growth of tumor.

CASE 4. A 59-year-old Negro entered the hospital on February 15, 1949, complaining of intermittent diarrhea of 2 years' duration. He had been studied elsewhere, but no diagnosis was established until the patient himself felt a mass in the right side of the abdomen. He then consulted another physician, who carried out a barium enema, which revealed a large filling defect in the right colon. There had been only a slight loss in weight.

Physical examination disclosed a well preserved and well nourished man. There was a large fixed mass, about the size of an orange, in the right lower quadrant of the abdomen, and slight abdominal distention.

Examination of the blood showed a hematocrit of 39 per cent and a white-cell count of 8000. The urine was normal. The total serum protein was 6.2 gm. per 100 cc.

After 6 days of preparation with Sulfasuxidine, a right colectomy with excision of a segment of the terminal ileum was performed. There was a large bulky tumor in the ascending colon; the terminal ileum was adherent to it, and there was seeding of tumor on the serosa of the adjacent ileum. The regional lymph nodes were heavily infiltrated with tumor. However, there was no demonstrable peritoneal or pelvic seeding, and the liver was small, smooth and apparently free of metastases. It was easy to obtain a good margin of mesentery beyond the involved lymph nodes.

Convalescence was uneventful, but the patient was dead within 10 weeks of the operation from a massive metastatic growth of cancer in the liver. At post-mortem examination the liver weighed 4700 gm.

Here was a patient with what appeared clinically to be a slowly growing tumor: a two-year history, a large palpable tumor and, despite lymph-node involvement, no palpable metastases to the liver and no appreciable enlargement of that organ. After extirpation of the primary lesion, hepatic metastases developed at an extraordinary rate of speed. Indeed, the clinical picture two months after operation was more suggestive of plasma hepatitis than of metastatic cancer. In such circumstances it is impossible to avoid the conclusion that this operation precipitated the rapid death, perhaps by the forcing of tumor cells into the portal vein when the tumor was manipulated. If so, however, one must postulate that the liver was more fertile soil for the cells than the original location in the colon.

Moreover, it is not only surgery that contributes to these explosive outbursts of cancer. The manner in which recurrent cancer of the bowel may remain localized for several years and then, within the space of a few weeks, bring about the death of the patient is well known.[6] Metastatic, malignant melanomas often behave in a similar fashion, remaining quiescent for years after the primary excision and then suddenly, within a matter of weeks, producing numerous, huge metastases in many different viscera. The question to be answered is

not what makes the cells suddenly grow but what has held them in abeyance for so long.

Discussion

Although the 2 cases in which spontaneous regression occurred are unusual, the other cases described above are typical of the manner in which neoplastic disease behaves on many occasions. Indeed, if one follows each patient with "hopeless" cancer carefully, one gains the impression that, as a rule, the progress of the disease is interrupted by periods of arrest if not regression, followed in turn by periods of more or less rapid growth. Certain deductions that may be drawn from these observations merit a brief consideration.

The only recognized method of treating cancer today is the total destruction of the lesion by either radiation or operation before it has metastasized. Yet one cannot ignore the fact that apparent cures (ten-year arrests or longer) may be obtained without the destruction of every cancer cell (Cases 1 and 3), and contrariwise efforts to destroy the parasite cancer may only break down the defenses of the host, as in Case 5. Unfortunately, at present there is no way to assay the biologic propensities of a given tumor before operation, and the surgeon is reduced to the necessity of carrying out what is known as best for the greater number — namely, the most radical excision possible in every case. However, with increasing interest in the biologic behavior,[7, 8] as well as the histologic appearance, of neoplasms it may be possible at some future date to select for radical surgery only patients who can be benefited and to avoid radical operation when it will do more harm than good. Most desirable of all, it may be possible to determine the growth curves of a given tumor so as to plan extirpation at periods of quiescence rather than during periods of very active growth. In this connection attempts to slow the growth rate of highly malignant neoplasms by preoperative x-ray therapy requires more careful evaluation.

Unfortunately, these theoretical considerations are of little value at the moment, but meanwhile there are some practical lessons to be drawn from observations on the natural course of a given cancer. In planning treatment the surgeon should assay the biologic behavior of each neoplasm, so far as it is possible, from the known course of the lesion as evidenced by history, physical examination and x-ray study. Several examples are worthy of emphasis. The first is the matter of recurrence. Whenever a cancer recurs locally or as a solitary metastasis a year or longer after an initial operation, reoperation, even if it entails a procedure of great magnitude, is proper. The mere fact that a recurrence appears as a localized lesion is a sort of a biologic test suggesting a high degree of natural resistance to the growth and warranting a second attempt at extirpation. The length of time that has elapsed since the initial operation is of great significance. The longer the period of freedom after which a solitary metastasis appears, the more radical one can be in advising reoperation. In very early recurrence, on the other hand, it is better to observe the course of the lesion for a while since numerous, inoperable metastases may appear elsewhere and make any surgery unwise. Secondly, the huge, locally "inoperable" tumor without lymph-node or distant metastases presents a major challenge to the surgeon. Here, again, is evidence of great natural resistance so that if the growth can be extirpated, the prognosis should be excellent. Under such circumstances considerable risk is justifiable.

In lesions that have spread beyond the reach of surgical resection the situation becomes very complex. The excellent results that sometimes follow palliative resection make it proper to excise the primary lesions in practically all cases. Certainly in gastrointestinal lesions this should always be done. However, if it is not possible to extirpate metastases completely, it seems reasonable to limit the resection to the local, primary lesion, in the hope, thereby, of avoiding unnecessary spread of the disease and of preserving whatever natural resistance the regional lymph nodes may be able to muster. The possible role of the lymph nodes in preventing the spread of a primary lesion has been given very little attention by surgeons. In general, the lymph nodes are viewed as passive receptors of the active neoplasm. Wide lymph-node dissection in conjunction with excision of primary growth is regarded as essential for adequate cancer surgery. However, in cancer of the face and tongue there is some reason to believe that the excision of the regional lymph nodes at the same time as the primary lesion is less effective than when it is delayed for some time. It is reasoned that thereby the nodes are allowed to pick up cancer cells that are in transit at the time of the initial operation and that, in the absence of the lymph nodes, would spread more widely. In the present state of knowledge, one hesitates to apply this reasoning to cancer in other regions of the body, but as more becomes known about the biology of particular tumors, it may prove a very fruitful approach.

The fact that the rate of growth of metastatic lesions varies in different locations in the body is of great significance. One should not hesitate to operate upon painful or rapidly progressing recurrences in one portion of the body merely because there are known metastases elsewhere. If the distant metastases appear to be slowly progressive, it is reasonable to excise a rapidly growing local recurrence, assuming, of course, that it is technically possible, as in Case 4. Many months or even years of comfort may follow such operations.

So far as nonsurgical methods of treating cancer are concerned, the need for a careful appraisal of the biologic behavior of any individual tumor as-

sumes even greater importance. The use of hormones in the treatment of metastatic breast cancer is an excellent example. The mere fact that a given breast lesion appears to be unfavorable is not sufficient grounds on which to advocate the use of hormones. Since it is known that metastatic breast cancer may remain dormant for years without treatment, it is meddlesome to employ hormonal agents, whose action is unpredictable and at best only palliative until one knows precisely what a given tumor is doing. Conceivably, the use of either estrogens or androgens might activate a lesion that otherwise would have remained quiescent. Except for experimental studies, the use of hormones at present should be restricted to established lesions that are obviously progressive as manifested by the history and x-ray or physical findings. Under such circumstances, the effect of therapy can be promptly evaluated and to some extent controlled by the subsequent behavior of the tumor.

The same argument can be advanced against the routine use of radiation after radical surgery. Until more precise information regarding the behavior of a specific tumor is available it seems more reasonable to await recurrence and to treat it vigorously than to employ routinely a light dose of x-ray not calculated to destroy an established tumor anyway. Moreover, who can say that in certain cases radiation therapy may not favor rather than reduce the chances of reactivation of tumor?

It follows that whenever a given tumor that is beyond radiation or surgical extirpation appears from the clinical evidence to be quiescent and asymptomatic it is reasonable to observe it rather than to attempt to treat it by means that at best would only prove palliative. If, under observation, symptoms appear or the lesion progresses, palliative radiation, chemotherapy or hormonal therapy should be given a trial.

Finally, in the evaluation of any new methods of cancer therapy it is obvious that occasional temporary regressions or arrests of tumors cannot be interpreted as evidence of a successful response to a particular agent unless it is consistently observed in many different cases.

Summary

Evidence is presented to show that cancer is not invariably a steadily progressive process. It may undergo spontaneous regression and is often subject to temporary arrests, and when it metastasizes the rate of growth of the same tumor varies widely in different locations. The theoretical and practical significance of these observations is discussed.

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CHLOROMYCETIN IN THE TREATMENT OF SALMONELLA ENTERITIS*

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SALMONELLA infections have shown a singular refractoriness to chemotherapeutic and antibiotic agents thus far. The inability of sulfonamides to affect favorably the course of the disease is now well established.[1] During the past year, 8 cases of salmonella enteritis were treated at Children's Hospital, Washington, D. C., with streptomycin in large doses.[2] Only 1 patient was rendered permanently free of salmonella; in the other 7 cases, the organism reappeared in the stools after discontinuation of therapy. Seligmann et al.[3] have similarly reported a series of 5 cases of salmonella enteritis in infants in whom streptomycin failed to produce a permanent bacteriologic cure.

Preliminary trials with aureomycin and aerosporin (polymyxin B) in salmonella enteritis have also proved unsuccessful in our hands.

Because of the disappointing results thus far with all previous therapy, it was deemed of considerable interest to treat a series of cases of salmonella enteritis with Chloromycetin. This was predicated on the ready susceptibility of the organism to this drug since the majority of strains of salmonella are inhibited by Chloromycetin in concentrations ranging from 2 to 5 microgm. per cubic centimeter. The successful use of Chloromycetin in typhoid fever reported by Woodward et al.[4] gave added impetus to the belief that this antibiotic might similarly prove to be efficacious in salmonella infections in view of the close bacteriologic relation of the organisms. As yet, there have been no reports in the literature describing the use of Chloromycetin in salmonella enteritis.

During the past five months, we have had the opportunity of using the drug in the treatment of 9 infants with this infection. The present report discusses the clinical and bacteriologic observations made in these cases.

MATERIAL

In all 9 patients the infection appeared to be limited to the gastrointestinal tract, and no systemic spread occurred in any of them. In every case the chief complaint on admission was diarrhea ranging from three to eleven days in duration prior to entry. In 6 patients there was an associated fever at the time of hospitalization. When first admitted to the ward, 4 of the infants appeared moderately ill, and the other 5 were regarded as having a mild illness. The age of the patients ranged from two to twenty-four months. Seven were white, and 2 were Negroes.

METHOD OF STUDY

A brief description of the bacteriologic methods used in this investigation is pertinent. During the past two years, a special ward for the study of diarrhea has been set up at Children's Hospital to investigate the efficacy of antibiotics in both specific and nonspecific enteritis. All patients admitted with diarrheal disease are sent directly to this ward, and three consecutive daily stool cultures are obtained routinely. Only in this way can the sporadic case of salmonella enteritis in infants be detected since the diarrheal manifestations are often mild and self-limited and simulate closely the much more frequently encountered cases of nonspecific enteritis.

After the rectal-swab cultures were obtained, they were immediately streaked at the bedside on Salmonella–Shigella (SS) agar and desoxycholate citrate (DC) agar and incubated for twenty-four hours. In addition, Kauffman's tetrathionate broth was seeded with the rectal swab and subcultured on SS plates after eighteen to twenty-four hours of incubation. Colorless colonies from SS and DC mediums were subcultured into Kliger's iron agar, and identification of the organisms was performed with the use of group-specific O serums.|| In questionable cultures, sugar broths, examination for motility, indole formation and other biochemical identification procedures were employed.

The distribution of the various types of salmonella in this series was as follows: *Salmonella Newport*, 3 cases; *S. typhimurium*, 2 cases; and *S. Kentucky*, *S. Zagreb*, *S. San Diego* and *Oranienberg*, 1 case each.

During the course of treatment, daily stool cultures were taken, and after termination of therapy, cultures were obtained at weekly intervals in the follow-up clinic. A total of 190 stool cultures were performed in this series (an average of 21 per pa-

*From the Research Foundation, Children's Hospital.
This study was supported by a grant from the Antibiotic Study Section of the Division of Research Grants and Fellowships, The National Institutes of Health, United States Public Health Service.
Chloromycetin was supplied by the Parke–Davis Company, Detroit, Michigan.

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||We are indebted to Lieutenant Colonel L. R. Kuhn, of the Army Medical Center, Washington, D. C., for confirmation and final identification of the organisms by the use of type-specific H serums.

tient), of which 88 were positive for salmonella. Of these, tetrathionate broth yielded a positive culture in 84 specimens, SS agar in 50, and DC agar in 29. In the majority of the cultures, the organism was recovered from 2 or all 3 mediums simultaneously. However, in 38 out of 88 positive cultures, salmonella was isolated from only 1 culture medium in spite of the fact that the stool specimen was inoculated in the 3 mediums simultaneously. Of these, tetrathionate broth exclusively yielded a positive culture in 36 cases, whereas positive cultures were isolated solely on SS agar in 2 specimens and DC agar in none. Summarizing our total experience in evaluating stool culture mediums in salmonella in the past eighteen months, during which a total of 17 patients have been carefully followed with daily stool cultures totaling 350 for the entire series, we found that in 71 cultures only 1 of the 3 mediums grew out a positive culture; tetrathionate broth yielded it exclusively in 64 (90.1 per cent), SS agar in 5 (7 per cent) and DC agar in only 2 (2.9 per cent). This serves to emphasize unequivocally the superiority of Kauffman's tetrathionate broth in the isolation of the salmonella organism from the stool.

TABLE 1. *Dosages and Blood Chloromycetin Levels in 7 Patients.*

PATIENT	DOSE OF CHLOROMYCETIN PER 24 HR.	NO. OF CHLOROMYCETIN LEVELS OBTAINED	AVERAGE CHLOROMYCETIN BLOOD LEVEL
	mg./kg. of body weight		*microgm./cubic centimeter*
J. P.	125	3	7.8
J. C.	187	5	6.6
H. S.	214	5	28.0
E. H.	250	4	40.0
R. W.	260	4	64.0
T. R.	285	4	79.0
J. S.	480	4	80.0

DOSAGE AND MODE OF ADMINISTRATION OF CHLOROMYCETIN

The dose of Chloromycetin ranged from 0.75 to 3.0 gm. per day in a four-hour divided dosage schedule. On a weight basis, this amounted to 110 to 480 mg. per kilogram of body weight per twenty-four hours. It is well to point out that the dosage employed in this series was purposely much higher than the 50 mg. per kilogram of body weight per day currently recommended for adults.[5] This was predicated primarily on the fact that infants ordinarily require considerably larger doses of an antibiotic to achieve a given blood level because of the greater rapidity of excretion of the drug. In addition, it was considered advisable to avoid the possibility of administering subcurative doses and hence to attempt to forestall the development of the carrier state. In spite of these large doses, no toxic manifestations were observed.

Chloromycetin was given for an interval ranging from nine to eighteen days, or an average of thirteen and eight-tenths days per patient. The total dose varied from 9.5 to 52 gm., with an average of 25.2 gm. per patient.

Spot blood assays taken just before the next dose was due on every second or third day in the majority of infants revealed Chloromycetin levels ranging from 3.8 to 180 microgm. per cubic centimeter. Table 1 presents the dosages and the resulting blood levels in 7 of the 9 patients in this series. The blood levels represent the average of 3 to 5 assays obtained during the course of therapy. It will be noted that the Chloromycetin assays were greatly in excess of the sensitivity of the organism.

Regarding the administration of Chloromycetin orally in the infant age group, it was found necessary to empty out the contents of the capsule, and, in view of the extreme bitterness of the drug, to administer it in different palatable vehicles in

TABLE 2. *Summary of 9 Cases of Salmonella Enteritis Treated with Chloromycetin.*

CASE NO.	PATIENT	AGE	ETIOLOGIC ORGANISM	CHLOROMYCETIN SENSITIVITY		DOSAGE OF CHLOROMYCETIN		
				BEFORE TREATMENT	AFTER RELAPSE	PER 4 HR.	PER 24 HR.	TOTAL
		mo.		*microgm./cc.*	*microgm./cc.*	*gm.*	*mg./kg. of body weight*	*gm.*
1	E. H.	16	*S. Newport*	5	5	0.5	250	42.0
2	H. S.	24	*S. Newport*	5	5	0.5	214	37.5
3	M. C.	12	*S. Newport*	2	—	0.25	132	9.3
4	J. S.	18	*S. Typhimurium*	5	5	0.5	480	52.0
5	R. N.	7	*S. Typhimurium*	5	5	0.25	130 260	42.0
6	J. P.	4	*S. Oranienberg*	5	5	0.125	125 250	10.5
7	J. C.	2	*S. Kentucky*	5	5	0.125	187	13.5
8	M. H.	6	*S. San Diego*	5	—	0.125	110	11.3
9	T. R.	18	*S. Zagreb*	5	5	0.25	285	41.5

*Chloromycetin blood level not determined.

an effort to disguise the taste. These included syrup of yerba santa, chocolate milk, chocolate syrup, cherry syrup and applesauce. After trying these various vehicles, we concluded that a mixture of Chloromycetin and syrup of yerba santa followed by chocolate milk was perhaps the least offensive method of oral administration in small children. Not infrequently, a moderate degree of anorexia accompanied the administration of Chloromycetin; however, the infant regained his appetite shortly after discontinuation of the drug.

Results

The pertinent data on the nine cases of salmonella enteritis treated with Chloromycetin are summarized in Table 2.

The results were not singularly gratifying. Of the 9 cases treated, only 2 showed continued negative stool cultures after a four-month follow-up period. In the other 7 patients, a transitory period in which the stool cultures were negative was observed, but within five to forty days after termination of therapy, the cultures once again became positive for salmonella. There was no attendant clinical exacerbation associated with these bacteriologic relapses. The relatively long negative intervals prior to cultural reversal in several of the patients serve to emphasize the desirability of obtaining repeated stool cultures during the follow-up period (tetrathionate broth being used as the culture medium) to avoid any abortive claims of "cures" in this disease.

Daily stool cultures obtained during the course of therapy permitted the observation that the number of positive stool cultures after the initiation of Chloromycetin ranged from 1 to 11, with an average of 6 per patient. There appeared to be no correlation between the strain of salmonella and the rapidity of its disappearance from the stool during therapy. Similarly, there was no demonstrable correlation between the dose of Chloromycetin and the results of therapy (Table 2). Thus, with the same strain (*S. Newport*) 1 patient (Case 3) received 132 mg. per kilogram of body weight per day, resulting in a rapid clearing of the pathogen from the stool within three days with no relapse. On the other hand, another patient (Case 1) was given 250 mg. per kilogram of body weight per day, and nine days elapsed before the stool culture became free of salmonella. In spite of the inordinately large dose of the drug in this patient, the organism reappeared in the stool within twenty-eight days.

It is difficult to explain these disappointing results with Chloromycetin in salmonella enteritis. Prior to therapy, the Chloromycetin sensitivities of the various strains of salmonella ranged from 2 to 5 microgm. per cubic centimeter. This places the organism among the relatively sensitive group of bacteria susceptible to the drug. Of singular interest was the observation that in no case was any increase in Chloromycetin resistance noted when the pathogen reappeared in the stools after termination of therapy. Thus, the failure of Chloromycetin in salmonella enteritis can hardly be explained on the basis of acquired resistance of the organism.

Of the 7 patients who relapsed, 2 were re-treated with the drug in a dosage twice as large as that used during the first course of therapy. The stools once again became negative for salmonella during the treatment interval. However, bacteriologic reversals occurred a second time four to ten days after the drug was discontinued.

All 9 patients in the series recovered clinically, with a rather prompt cessation of diarrhea and general improvement in nutritional status at the time of discharge. The part played by Chloromycetin in this clinical improvement is difficult to assess in view of the fact that a considerable number of untreated cases of salmonella enteritis

Table 2 (*Continued*).

Case No.	Duration of Treatment	Interval between Start of Treatment and Negative Stool Culture	Interval between Discontinuation of Treatment and Positive Stool Culture	Average Chloromycetin Blood Level	Outcome
	days	*days*	*days*	*microgm./cc.*	
1	14	9	28	40.0	Recurrence
2	12	4	40	28.0	Recurrence
3	9	3	(No relapse)	—*	Cure
4	18	9	25	80.0	Recurrence
5	14	1	8	64.0	Recurrence; patient re-treated with double initial dose, with second recurrence.
		2	10		
6	14	11	26	7.8	Recurrence; patient re-treated with double initial dose, with second recurrence.
		8	4		
7	18	6	30	6.6	Recurrence
8	15	1	(No relapse)	—*	Cure
9	14	10	5	79.0	Recurrence

managed with adequate supportive measures will run a mild, self-limiting course, provided no complications such as meningitis, septicemia and pneumonia supervene. It is entirely possible, albeit conjectural, that Chloromycetin serves a useful function in this disease by virtue of its transiently favorable effect bacteriologically during the acute phase of the illness. By the time a cultural relapse occurs, the infant's general condition is usually no longer in jeopardy, and a protective immunity may have been established. The carrier state in salmonella enteritis is undoubtedly a less hazardous phase than the acute invasive stage.

Comparison Between Streptomycin and Chloromycetin

During the spring and summer of 1948, we treated 8 cases of salmonella enteritis with large doses of streptomycin. Three patients received the drug orally alone, and the other 5 were given the antibiotic both orally and intramuscularly. The interval of treatment varied from ten to fourteen days. The age group of these children and the severity of illness were comparable to the present series of 9 cases treated with Chloromycetin. Table 3 summarizes the comparative response to therapy in the two groups.

Table 3. *Comparison between Streptomycin and Chloromycetin in the Treatment of Salmonella Enteritis.*

Drug	No. of Cases	Average Interval between Start of Treatment and Negative Stool Culture	Average Interval between Discontinuation of Treatment and Positive Stool Culture	No. of Relapses	No. of Deaths
		days	*days*		
Streptomycin	8	4	5	7 (87.5%)	0
Chloromycetin	9	6	23	7 (77.7%)	0

It may be generally stated that an inhibitory effect on both the salmonella organisms and the normal stool flora was observed during the period of administration of both drugs. The average interval required for the stools to become free of salmonella was four days after streptomycin therapy was started and six days after Chloromycetin therapy. There were 7 bacteriologic relapses out of 8 cases treated with streptomycin, and the same number out of the 9 patients managed with Chloromycetin showed a cultural reversal. A statistically significant difference, however, was observed in the interval between the discontinuation of therapy and the reappearance of the pathogen in the stool. In the streptomycin-treated group, the stools once again became positive within an average of five days of termination of treatment. On the other hand, in the patients treated with Chloromycetin, an average of twenty-three days elapsed before the salmonella organism reappeared in the stools. In 1 case, an interval of forty days had passed before the stool again became positive. The significance of this delayed reappearance of salmonella in Chloromycetin-treated cases is not apparent.

In both groups, the various strains of salmonella were quite susceptible in vitro to both drugs prior to initiation of therapy. After the bacteriologic reversal in both series, the organisms showed no particular increase in resistance to either drug when compared with those isolated before treatment was started. There was uneventful clinical recovery in both groups of cases. The contribution of either drug in the treatment of salmonella enteritis during the acute phase is difficult to determine. There appeared to be some indication from the 17 cases observed that the acute stage of the disease was possibly attenuated by these two drugs in the majority of cases. However, it was equally apparent that, except for a transitory sterilization of the bowel of its pathogen during the treatment phase and for varying intervals thereafter, neither drug was capable of effecting a permanent cure bacteriologically except in a small percentage of cases.

Summary

Nine cases of salmonella enteritis in infants were treated with Chloromycetin. The Chloromycetin sensitivities of the various strains of salmonella isolated from these patients ranged from 2 to 5 microgm. per cubic centimeter.

In spite of the ready susceptibility of the organism to the drug, only 2 of the 9 patients in this series became permanently free of the pathogen after treatment. In the other 7 cases, a transitory inhibitory effect on both the salmonella organism and the normal stool flora was observed; however, within five to forty days after Chloromycetin was discontinued, the pathogen reappeared in the stools. No increase in Chloromycetin resistance was observed in any case after bacteriologic relapse.

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TREATMENT OF TYPHOID FEVER WITH CHLOROMYCETIN

Report of Four Cases

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IN THE summer of 1949, 4 patients with typhoid fever were admitted to Belmont Hospital. All were treated with Chloromycetin. One patient (Case 4), a forty-four-year-old woman who died less than forty-eight hours after admission, had other conditions that were responsible for her death. The other 3 cases responded dramatically to Chloromycetin.

The first patient had an acute attack of typhoid fever. The second patient was the sister of the first and was asymptomatic; this case was discovered as a result of routine stool examinations. The third patient had been treated previously at another hospital and had a relapse of symptoms. Thus, treatment was given to patients in the acute, carrier and relapse stages of typhoid fever.

CASE REPORTS

CASE 1. M. F., a 14-year-old schoolgirl, was well until 12 days before admission, when she complained of headache and fever. She continued to have fever and began to have 5 to 6 watery stools each day. She was admitted to another hospital on July 7, 1949, where physical examination revealed an acutely ill, 180-pound girl with a temperature of 104°F. and a pulse of 80. There were no other abnormalities.

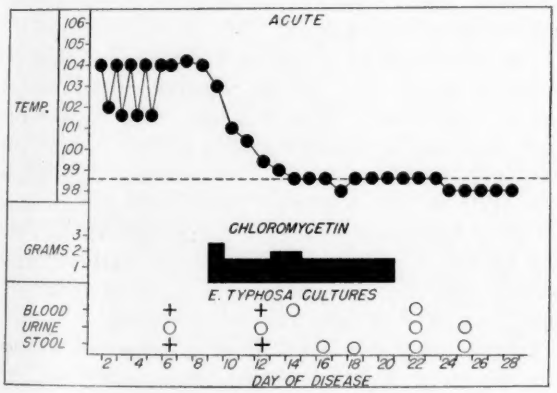

FIGURE 1. *Effect of Chloromycetin Therapy in Case 1.*

The temperature continued to be elevated to 104°F. in spite of penicillin begun on July 8 and Streptomycin begun on July 10. She had several loose stools daily. On July 11 blood culture was reported as positive for *Eberthella typhosa*, and Chloromycetin therapy was begun. The temperature dropped to 101°F. within 24 hours, and the number of bowel movements decreased. She was transferred to Belmont Hospital on July 13.

Physical examination showed an obese, lethargic girl with a temperature of 100.4°F. and a pulse of 90. No specific abnormalities other than an irregular erythematous rash on the abdomen were noted. The spleen was not palpable.

Examination of the blood disclosed a red-cell count of 4,300,000 and a white-cell count of 6950, with 59 per cent neutrophils and 41 per cent lymphocytes. Blood and stool cultures taken 48 hours after Chloromycetin therapy was begun were positive for *E. typhosa*. Agglutination for typhoid O was positive in a dilution of 1:160, and that for typhoid H was positive in a dilution of 1:160.

Chloromycetin was given for 11 days. One gram was given initially followed by 0.25 gm. every 3 or 4 hours to a total of 18 gm. Medication was continued for 7 days after the temperature had become normal; the effect of Chloromycetin is shown in Figure 1. The patient had an uneventful hospital course with no vomiting or diarrhea. Blood, urine and stool cultures were negative at weekly intervals for 3 weeks after cessation of therapy. The patient remained asymptomatic and was discharged on August 10.

CASE 2. L. F., a 10-year-old sister of the patient in Case 1, had a stool culture reported positive for *E. typhosa* on July 25, 1949. She had no fever, diarrhea or other symptoms and was discovered as a result of the routine checkup on the family. Physical examination on July 26 showed a healthy, afebrile girl with no significant physical abnormalities. Laboratory studies revealed a positive stool culture for *E. typhosa*. The white-cell count was 5950, with 51 per cent neutrophils and 41 per cent lymphocytes. Agglutination for typhoid O was positive in a dilution of 1:40, and that for typhoid H was positive in a dilution of 1:40.

She was given 2 gm. of Chloromycetin immediately and 0.25 gm. every 3 hours, to a total of 18 gm. At no time did she have fever, diarrhea or other clinical evidence of infection. Subsequent blood, stool and urine cultures on three consecutive occasions at weekly intervals were negative (Fig. 2). She was discharged afebrile and asymptomatic on August 20.

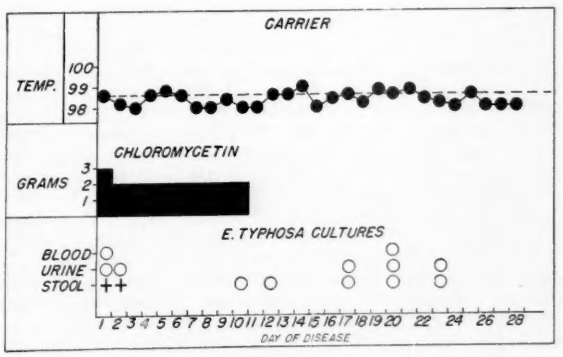

FIGURE 2. *Effect of Chloromycetin Therapy in Case 2.*

CASE 3. G. D., a 17-year-old boy, was treated at another hospital for typhoid fever from July 6 to July 29, 1949. Chloromycetin, 1 gm. three times each day, was given for a total of 10 days. Stool cultures were allegedly negative after treatment. On August 2 the patient had a chill followed by numbness of his hands. He became acutely ill, with headache, chills and fever. He vomited twice and had some stiffness of his neck. Chills, headache and sweating were

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more marked on the day of admission. He vomited six times and had watery stools. He was referred to the hospital with the diagnosis of a relapse of typhoid fever.

Physical examination revealed an acutely ill boy whose temperature was 104°F., with a pulse of 90. The spleen was palpable 1 cm. below the left costal margin. Laboratory studies showed blood and stool cultures positive for *E. typhosa*. Agglutination for typhoid O was positive in a dilution of 1:160, and that for typhoid H was positive in a dilution of 1:80.

The patient was given 4 gm. of Chloromycetin immediately and 0.5 gm. every 3 hours thereafter to a total of 20 gm. Intravenous administration of fluids was required for the first 24 hours. Within 36 hours of the beginning of Chloromycetin therapy, the temperature was normal, and there were no further loose bowel movements (Fig. 3). Rose spots

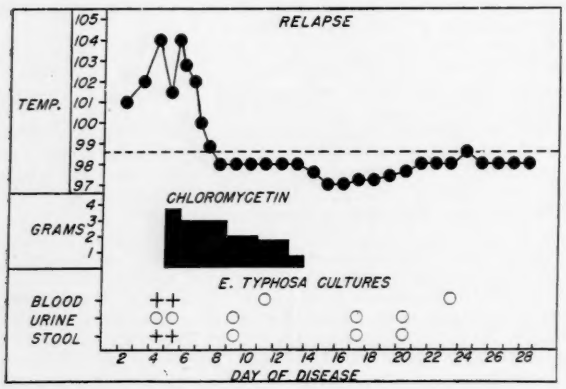

FIGURE 3. *Effect of Chloromycetin Therapy in Case 3.*

appeared on the chest and abdomen on August 5 and lasted for 48 hours. Convalescence was uneventful, and three consecutive weekly urine and stool cultures were negative after cessation of therapy.

CASE 4. R. F., the mother of the patients in Cases 1 and 2, had chills, fever, anorexia and vomiting beginning 3 weeks before admission. These symptoms subsided after a few days, and she remained well until 1 week before admission, when she had difficulty in breathing. She was admitted to another hospital on July 23. Physical examination showed an extremely obese, 44-year-old woman with dyspnea. The temperature was 103.4°F., the pulse 104, and the respirations 34. The blood pressure was 165/90. There was a Grade II systolic murmur with occasional extrasystoles. There were moist inspiratory rales over the right-lung base. The abdomen was so obese that it could not be examined. The extremities showed slight pitting edema of ankles. A diagnosis of an atypical pneumonia or cardiac insufficiency complicated by obesity was made. Examination of the blood revealed a white-cell count of 6300, with 45 per cent neutrophils and 43 per cent lymphocytes. The blood sugar was 161 mg., and the nonprotein nitrogen 31 mg. per 100 cc. Agglutination for typhoid O was positive in a dilution of 1:320, and that for typhoid H in a dilution of 1:40. A chest x-ray film was unsatisfactory owing to the patient's size. When the agglutination tests were reported on July 25, Chloromycetin therapy was begun but most of the drug was vomited. The patient was transferred to Belmont Hospital on the afternoon of July 26.

Physical examination revealed a woman weighing approximately 600 pounds who breathed rapidly even in the sitting position. The chest showed coarse rhonchi scattered throughout both lung fields. The heart demonstrated no murmurs, and the rhythm was regular. Examination of the abdomen was impossible because of obesity. There were scars of healed ulcers on the legs but no edema.

The temperature was 102.4°F., the pulse 126, and the respirations 44. The blood pressure was 200/100.

Examination of the blood disclosed a red-cell count of 3,700,000, with a hemoglobin of 12 gm., and a white-cell count of 6900, with 63 per cent neutrophils and 37 per cent lymphocytes. The urine had a specific gravity of 1.023, and gave a +++ test for albumin; the sediment contained many granular casts. The blood Kahn test was negative. Blood and stool cultures taken on July 26 were positive for *E. typhosa*. Agglutination for typhoid O was positive in a dilution of 1:80, and that for typhoid H was positive in a dilution of 1:40.

The patient was roused with difficulty and did not know where she was. After blood and stool cultures had been taken, Chloromycetin therapy was begun. One gram every hour for 8 hours, followed by 0.5 gm. every 3 hours, was given. It was impossible because of the patient's unusual size to evaluate her physical status accurately. An electrocardiogram showed only a sinus tachycardia, and consultation with a cardiologist did not indicate the need for digitalization.

The patient took medication and liquids well. The temperature dropped slightly (to 101.8°F.), and the pulse slowed to 110 and the respirations to 30. She remained acutely ill however and was placed in an oxygen tent 15 hours after admission. Respirations became labored several hours later. The temperature rose to 107°F., and she died 29 hours after admission.

The exact cause of this patient's death was difficult to determine. Permission for autopsy was not obtained. Death occurred at 8 p.m. on the hottest day of the year, and heat stroke may have been partially responsible. The probable cause of death was heart failure secondary to pneumonia and typhoid fever. There was no evidence to suggest hemorrhage or perforation.

DISCUSSION

The source of infection in the 3 cases occurring in the same family was presumed but never proved to be a polluted well in another state, which all 3 patients had visited a week before the onset of their illnesses. The source of the infection in the patient who relapsed is unknown.

The diagnosis in 3 out of 4 cases was made by positive blood and stool cultures taken within twenty-four hours of admission. The carrier patient had only a positive stool culture. No patient had ever had typhoid inoculations. Agglutination tests in the acute case and in the patient who relapsed had reached a level of 1:160 for the O antigen by the second week. The carrier patient, three weeks after the discovery of a positive stool culture, had an O antigen titer of only 1:40.

Chloromycetin was given in a dosage of 50 mg. per kilogram of body weight immediately and 50 mg. per kilogram per day thereafter to a total of 18 to 20 gm., or until the temperature had been normal for seven days. These dosages are in agreement with those recommended by Woodward et al.,[1, 2] who found that Chloromycetin should be given for at least eight days to prevent relapses. In the case reported by Foster and Condon[3] there was complete remission of fever ninety-six hours after the administration of Chloromycetin, with no relapse.

In the cases reported above the temperature became normal, and blood and stool cultures were normal within seventy-two hours of the beginning of Chloromycetin therapy. No toxic reactions or side effects were noted from the drug. A high-calorie, smooth diet was given to all patients. No

patient was discharged until three consecutive negative stool and urine cultures at weekly intervals were obtained. Further cultures will be obtained by the city or state department of health.

Summary

Chloromycetin appears to be effective in the treatment of the acute, carrier and relapse stages of typhoid fever. One case of each type is presented in detail.

The patient in relapse had been treated with Chloromycetin for ten days during his initial attack. The relapse occurred four days later and was associated with positive blood and stool cultures for typhoid bacilli.

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MEDICAL PROGRESS

ANTICOAGULANTS*

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WHEN a blood vessel has been severed the prompt coagulation of blood is an essential safeguard against fatal hemorrhage. Yet the same defense mechanism may itself threaten life through the formation and propagation of an intravascular clot. Although heparin had been employed successfully as early as 1935 to prevent intravascular clotting, its brief duration of action and high cost discouraged general use. The discovery of Dicumarol stimulated enormous interest in the anticoagulant drugs and the ability of these agents to prevent thrombosis and embolism has now been established beyond doubt. It is equally well established that the careless administration of anticoagulants is always disappointing and sometimes disastrous. The purpose of the present review is to summarize the pharmacologic properties of heparin and Dicumarol and to indicate that knowledge of these properties is a prerequisite for their safe and effective use.

Mechanism of Intravascular Clotting

A discussion of drugs that decrease the coagulability of blood may properly begin with a description of the events that lead to the formation of a clot. Although the main steps in this process were established by Morawitz[1] and Fuld and Spiro[2] in 1904, recent investigators have postulated a bewildering number of accessory factors and reactions that may also participate in the clotting mechanism.[3] Many of these are as yet controversial and need not be considered here. The following discussion, though undoubtedly an oversimplification, should suffice for an understanding of the basic actions of the anticoagulant drugs and the methods used for controlling their administration.

Intravascular clotting begins with the adhesion of thrombocytes to the intima of a blood vessel commonly at a point where the endothelium has been injured. Contrary to earlier reports, the platelets are not stuck together by fibrin or its precursors. Indeed, normal agglutination of thrombocytes can occur in the complete absence of fibrinogen.[4] The "white thrombus" of platelets serves as a starting point for the true fibrin clot. As thrombocytes continue to pile up on the original clump, some of them disintegrate and release thromboplastin. In the presence of ionized calcium, thromboplastin converts inactive prothrombin to the active enzyme thrombin. At first this process is slow, and it is likely that the small amounts of thrombin initially formed are inactivated by the antithrombin normally present in plasma. But when sufficient thromboplastin has been liberated the thrombin begins to convert fibrinogen to fibrin. At the same time thrombin is thought also to transform another protein, plasma accelerator globulin, or ac-globulin, to serum ac-globulin, which in turn greatly increases the rate of thrombin liberation.[6]‡ In the presence of ac-globulin, therefore, the conversion of prothrombin to thrombin is autocatalytic; once initiated it rapidly gathers momentum, and the formation of fibrin from fibrinogen is correspondingly accelerated. As the network of fibrin strands extends out into the blood stream it begins to entrap not only more platelets but also leukocytes and erythrocytes, and the blood vessel may soon be oc-

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‡The accelerator globulin of Ware and his co-workers[5] is but one of a number of factors that have been described as hastening the production of thrombin from prothrombin. It is not clear how many of these are actually separate entities.

cluded by a typical clot. The steps just outlined are summarized diagrammatically in Figure 1.

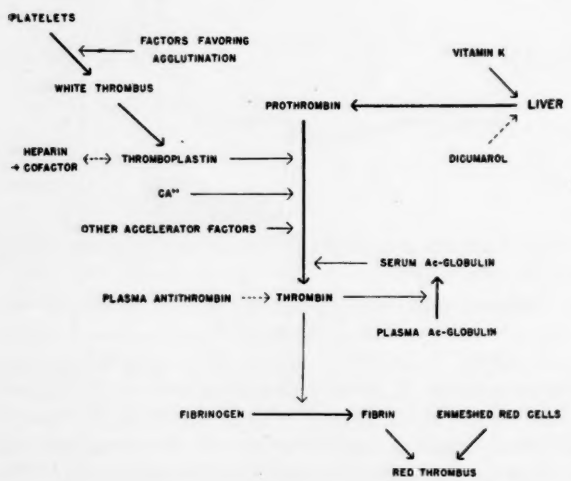

FIGURE 1. *Steps in the Formation of a Thrombus.*
The heavy solid arrows indicate actual transformations. The light solid arrows indicate acceleration, and the broken arrows indicate inhibition. "Factors favoring agglutination" include slowing of the blood stream, endothelial injury, thrombocytosis and probably certain changes in the composition of the plasma. Heparin may have actions other than the one indicated here.

HEPARIN

Heparin was discovered in 1916 by McLean,[7] a second-year medical student working in Howell's laboratory at Johns Hopkins University. In attempting to purify thromboplastic phosphatides from various tissues, McLean obtained a substance that not only failed to hasten coagulation but actually inhibited it. Howell's interest in the new substance was immediately aroused, and during the next several years he established its identity as a polysaccharide and described methods for its extraction and purification.[8] Because of its comparatively high concentration in liver it was named heparin. Howell noted its lack of toxicity and as early as 1917 suggested that it might be useful "in the therapeutic treatment of disorders of coagulation."[9] However, it was not until 1935 that purified heparin became available in sufficient amount for trial in human subjects, and the first clinical studies appeared in 1937,[10, 11] twenty years after Howell's original suggestion.

Chemistry

Heparin belongs to the group of polysaccharides of high molecular weight that also includes chondroitin sulfuric acid and mucoitin sulfuric acid. It differs from mucoitin sulfuric acid in containing not one but several sulfuric acid groups for each glucosamine-glucuronic acid pair. Charles and Todd[12] obtained a crystalline barium salt of heparin that they thought was pure and homogeneous. In their preparation the ratio of nitrogen to sulfur was 1:2.5, and they concluded that the fundamental unit of heparin consisted of two adjacent glucosamine-glucuronic acid pairs, one containing two and the other three sulfuric acid groups. However, Jorpes,[13] by fractionation of the brucine salt of heparin, has prepared samples that correspond to a mucoitin tri-sulfuric acid, and the structural formula of Figure 2 is written in accordance with this suggestion. Jorpes considers that the crystalline product of Charles and Todd[12] is a mixture of mucoitin di-sulfuric and tri-sulfuric acids. Indeed he doubts whether any heparin sample so far prepared consists of a single molecular species.

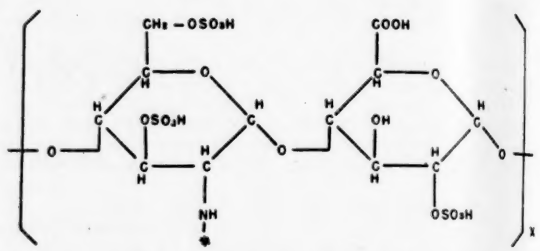

FIGURE 2. *Tentative Structural Formula for Heparin.*
The three hydroxyl groups esterified with sulfuric acid were chosen arbitrarily. Heparin is inactivated by freeing of the amino group, but the nature of its linkage, designated by an asterisk, has not been established. The degree of polymerization is also unknown.

The strongly acidic properties of heparin account for its ability to combine with proteins and to form insoluble salts with barium or with basic compounds of high molecular weight such as toluidine blue and protamine. Moreover, the sulfuric acid groups are essential for the activity of heparin, and the anticoagulant potency of different fractions from the same animal species tends to increase with increasing sulfuric acid content. However, heparins of approximately equal sulfur content but from different species differ considerably in potency.[14] Anticoagulant action is therefore not uniquely determined by the degree of esterification, but is also modified by other structural features, which vary from species to species.

Occurrence, Preparation and Standardization

When heparin reacts with toluidine blue, the color of the dye changes to purple. This color change, metachromasia, is specific for sulfuric acid esters of high molecular weight and can be demonstrated histologically — for example, in cartilage, which contains chondroitin sulfuric acid. But the strongest metachromatic staining occurs in the granules of Ehrlich's mast cells, which are distributed close to the capillaries in various tissues of

the body. Jorpes, Holmgren and Wilander[15] were able to correlate heparin content with the number of mast cells in various tissues and to show that during anaphylactic shock in the dog the liberation of heparin into the blood stream from the liver was accompanied by a disappearance of metachromatic granules from the hepatic mast cells. These observations have conclusively identified the mast cells as the site of formation of heparin. Their pericapillary location suggests that the secretion of heparin may help to maintain the fluidity of blood in certain vascular beds, but a physiologic function of this sort has not yet been clearly demonstrated.[13]

Lung tissue is particularly rich in mast cells, and beef lung is the present source of most commercial heparin. The ease with which heparin combines with proteins[16] makes its extraction and purification a complicated and expensive* procedure.

Since chemical standardization of heparin is untrustworthy, each new lot must be assayed for its anticoagulant activity. Howell defined 1 unit as the amount needed to prevent clotting in 1 cc. of cat's blood for twenty-four hours at 0°C., but such a definition is not sufficiently precise. In 1942 the Toronto group supplied the National Institute for Medical Research, London, with a large quantity of a highly potent sodium salt of heparin to be used as a provisional international standard. One unit is now defined as the activity of 1/130 mg. of this reference standard. It is equivalent to the Toronto or Connaught unit originally proposed in 1938 by Murray and Best[17] and corresponds to about 5 Howell units. In the United States commercial preparations of the sodium salt of heparin are adjusted to a potency of 100 units per milligram and are supplied in sterile solution containing 10 mg. (1000 units) per cubic centimeter.

Mechanism of Action

Heparin alone has little effect on the isolated components of the clotting system. For anticoagulant activity it requires a protein co-factor ("heparin complement"), which is present in the crude albumin fraction of plasma. The co-factor is probably not identical with the antithrombin of normal plasma,[18] nor is it present in pure crystalline albumin.[19] Loomis[20] believes it to be a euglobulin perhaps identical with fibrinolysin.

In heparinized blood the conversion of prothrombin to thrombin is prevented, and coagulation cannot occur.[21] Heparin therefore inhibits the first phase of the clotting process. However, if a large amount of thromboplastin is added, a clot promptly forms. Howell[22] originally postulated that heparin combines with prothrombin to form a complex from which heparin can be removed by an excess of thromboplastin. It is equally possible that heparin prevents the formation of thrombin by combining directly with thromboplastin so as to prevent it from activating prothrombin. In any event, the antagonism between heparin and thromboplastin is quantitative and mutual; an excess of either nullifies the action of the other.[23]

Since Ferguson[24] believes that serum tryptase participates in the activation of prothrombin, the ability of heparin to inhibit this proteolytic enzyme is of some interest.[25] But the concentration of heparin required is considerably greater than that which suffices to prevent clotting, and the anticoagulant action of heparin can scarcely be ascribed to tryptase inhibition. A definitive explanation of how heparin inhibits the first stage of the clotting process must await a fuller understanding of the complicated reactions concerned with the conversion of prothrombin to thrombin.

Heparin may also interfere with the second stage of clotting by inhibiting the enzymatic activity of thrombin. However, the ability of heparins from various species, and of synthetic polysaccharide esters of sulfuric acid, to inactivate thrombin does not parallel their anticoagulant potency,[26] and the antithrombic action of heparin is probably of secondary importance.

In their earlier investigations Best and his coworkers[27] found that high concentrations of heparin decreased the agglutination of platelets, and they concluded that heparin inhibits intravascular clotting chiefly by preventing the initial clumping of thrombocytes on the blood-vessel wall. This hypothesis has not been confirmed by subsequent experiments. Indeed, as first pointed out by Copley and Robb,[28] commercial samples of heparin may actually cause agglutination of platelets, both in vivo and in vitro. The platelet count may fall precipitously as the clumps of platelets are filtered out of the blood stream by the capillaries.[29] The agglutination is transient, and the platelets return to the circulating blood undamaged even while the anticoagulant effect of heparin is still present. This curious phenomenon is apparently not seen with all preparations of heparin, and is probably of little practical significance. It does demonstrate, however, that the therapeutic efficacy of heparin is due to inhibition of the clotting mechanism per se and not to any interference with the clumping of thrombocytes.

The anticoagulant action of heparin may be reversed almost instantaneously by basic substances that form poorly dissociated, insoluble salts of heparin. Two of these, toluidine blue and protamine, have been used clinically to combat hemorrhage due to an excess of heparin in the blood stream.[30]

Action of Heparin in Vivo

Heparin is inactive by mouth and must therefore be given parenterally. When a single dose is in-

*The current cost of 300 mg. of heparin, approximately the amount needed daily for treatment of the average patient, is $12.

jected intravenously the clotting time rises swiftly to a peak within about ten minutes. This slight delay in attaining maximum action is probably due to the time needed for combination with certain components of the clotting system, for the anticoagulant effect in vitro is enhanced by prior incubation of heparin with blood.[31] The prolongation of the clotting time depends on the concentration of heparin attained in the blood stream, the logarithm of the clotting time being a linear function of heparin concentration.[31] Thus, small doses of heparin cause little increase in clotting time, whereas

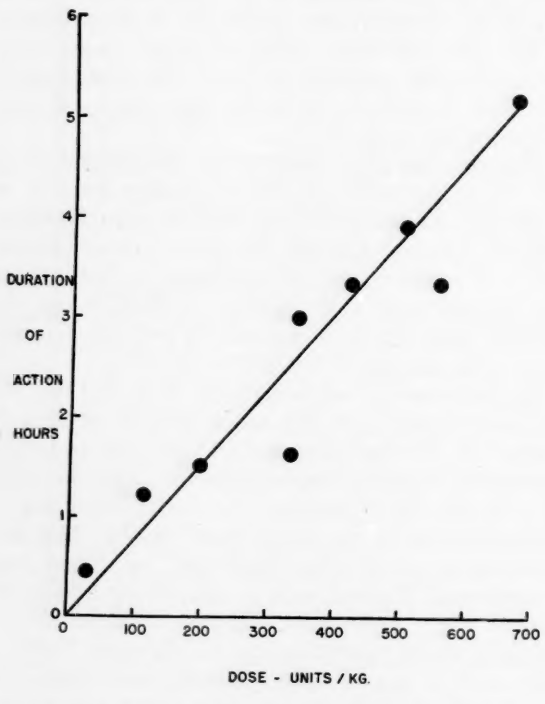

FIGURE 3. *Influence of Dose on the Duration of Action of Heparin in Dogs.*
The points are plotted from the data of Jaques.[32]

larger doses have proportionately much greater effects.

After the peak effect has been attained the anticoagulant action wanes rapidly. The total duration of action depends on the dose (Fig. 3), but even with large doses that initially produce a many-fold increase in clotting time, the heparin disappears within a few hours.[32] In the dog a small amount is excreted in the urine but only when the concentration of heparin in the blood is greater than 1 or 2 units per cubic centimeter.[26] In man, renal excretion of active heparin is probably unimportant.[33] However, an inactive degradation product, uroheparin, may be identified in the urine by its metachromatic reaction.[26] Jaques[34] has described an enzyme, heparinase, that may well account for the rapid disappearance of active heparin from the body. The linear decrease of blood heparin concentration with time described in the dog[31] also suggests destruction of heparin by an enzyme system with a limited capacity for substrate. Furthermore, even in vitro heparin is gradually destroyed, and clotting ultimately occurs. The evanescent action of heparin in the body constitutes one of the greatest problems in its clinical use.

Mode of Administration

Heparin concentrations sufficient at least to double or triple the clotting time are required for protection against intravascular thrombosis. To obtain a steady therapeutic effect Murray[35] has recommended continuous intravenous infusion of heparin in isotonic saline or glucose solution containing 0.2 mg. per cubic centimeter. For the average patient about 14 mg. per hour is sufficient, but the actual rate of infusion must be adjusted according to the effect on the clotting time determined every few hours. With this mode of administration it is possible to approach the ideal of maintaining a constant blood concentration, but the inconvenience of using a continuous intravenous drip, the necessity for immobilizing the patient in bed and the danger of infusing a large volume of fluid in patients with cardiac failure have limited the popularity of this technic.

In Sweden* the intermittent intravenous administration of heparin has received extensive and apparently successful clinical trial.[13] Single doses of 50 to 150 mg. are given every four to six hours during the day, with the last dose in the evening somewhat larger than the others. Usually none is given during the night. The total dose per day is approximately 400 mg. No attempt whatsoever is made to maintain a steady anticoagulant effect, and determination of the clotting time is seldom used as a guide to therapy. Indeed, the clotting time must fluctuate over an extraordinarily wide range, being markedly prolonged just after each injection and returning to normal some time before the next. At night there must be a period of several hours during which no anticoagulant action is present.[36] If this mode of administration actually proves to be as effective as continuous intravenous infusion, the formation and growth of thrombi must be a rather sluggish process easily held in check by intermittent inhibition of the clotting mechanism.

In this country attempts have been made to avoid the disadvantages of intravenous administration by the intramuscular administration of heparin in concentrated (10 per cent) aqueous solution.[37, 38] By this route absorption is slow enough so that the effect of a single dose often lasts for several hours, and the interval between doses may be prolonged correspondingly. By adjusting the dose

*Commercial heparin in Sweden is standardized to contain 80 units per milligram.

according to the effect on clotting time one can maintain an effective therapeutic level of heparin in the blood. The intramuscular route is preferred because subcutaneous injection frequently produces pain and induration. Serious or even fatal bleeding into the area where heparin has been injected often occurs in small laboratory animals,[39] but hemorrhage into the tissues at the site of injection has not been troublesome in man.

Still further prolongation of the effect of a single dose may be achieved with repository preparations. The deep subcutaneous deposition of 300 to 400 mg. of heparin in a special gelatin medium (the so-called Pitkin menstruum) has been enthusiastically advocated by Loewe.[40] At ordinary temperatures this preparation is a gel and must be liquefied by warming before it can be injected. By the separate administration of a portion of the dose in Pitkin menstruum containing epinephrine and ephedrine, Loewe has been able to maintain an anticoagulant effect for as long as two or three days. Severe pain, with swelling and tenderness, occurs at the site of injection and is sometimes accompanied by a febrile reaction. However, Loewe has recently stated that this very serious drawback can be overcome by careful buffering of the preparation to a physiologic pH.[41] Heparin in Pitkin menstruum may be given intramuscularly, but the duration of action of a single dose is shortened.

A disadvantage common to all the repository preparations is unpredictability. For example, in a group of 8 patients who were given a single intramuscular dose of 300 mg. of heparin emulsified in a mixture of cholesterol derivatives, peanut oil and beeswax, the maximum clotting time varied from 400 to 1400 per cent of the control value and the duration of therapeutic action varied from fifteen to twenty-four hours.[42] It is evident that none of the modes of administration in current use are completely satisfactory. Investigation of still other methods is needed. The success of procaine penicillin suggests that injection of an aqueous suspension of an insoluble heparin salt might be worthy of trial. Whatever method ultimately proves most advantageous, the effect on clotting time should determine what size and spacing of doses is most suitable for each patient.

Toxicity

Early preparations of heparin sometimes produced chills, fever, headache, nausea and vomiting. These reactions were due to impurities and are no longer encountered. Except for local irritation heparin is practically nontoxic. Rabbits have been given 500 mg. in a single dose intravenously without untoward effects. Despite its ready combination with protein, heparin is not antigenic in animals,[43] and allergic sensitization to heparin in man is very rare. In a review of the Swedish literature Jorpes[13] found only 4 cases of anaphylactic reactions. The only real danger of heparin administration, hemorrhage, is discussed in a later section.

(*To be concluded*)

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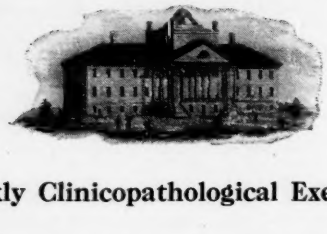
CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 36051

PRESENTATION OF CASE

A seventy-year-old Italian-born woman was admitted to the hospital because of a "sticking lump" in the throat.

The patient had been well until two weeks before admission, when she began to experience a sensation of "something in her throat." At this time she also noted a swelling in the front of the neck and an irritating, nonproductive cough. Her appetite was good, and she was able to swallow solids with no discomfort. A week before entry she began to suffer respiratory difficulty upon eating solids, and since that time had taken only liquids. Dyspnea became so severe that she could not sleep at night. She gave no history of heat or cold intolerance, palpitation or tremor. The menopause had occurred at the age of fifty-one.

Eight years before admission the patient underwent a panhysterectomy for an adenoacanthoma of the uterus. She had been followed in the Tumor Clinic since that time and had shown no evidence of recurrence.

Physical examination revealed a short, stocky, alert woman in moderate respiratory distress. The voice was not hoarse, but the cough was brassy. The facies was suggestive of myxedema, and the general habitus, of cretinism. The fingers were short and stubby. The palpebral fissures were narrow, with epicanthal folds. The skin was dry and leathery. The teeth were in poor repair, and only about half were present. There was a mild right dorsal kyphoscoliosis. In the anterior portion of the neck there was a fixed and stony-hard mass occupying the normal position of the thyroid gland. It dipped into the mediastinum and was surmounted at the left upper pole by a nodule measuring 1.5 by 1 cm. The veins over the upper chest were dilated. In the left paravertebral area near the scapula there were questionable bronchovesicular breath sounds, with no definite widening of the retrosternal dullness. There were no palpable lymph nodes. The heart was not enlarged to the left. The pulmonic second sound was greater than the aortic second sound. There was a Grade II pulmonic systolic murmur. The liver edge was just palpable beneath the right costal border, and in the lower midabdominal region there was an old longitudinal scar. The pelvic and rectal examinations were negative.

The temperature was 98.6°F., the pulse 100, and the respirations 32. The blood pressure was 110 systolic, 60 diastolic.

The urine was normal. The blood hemoglobin was 10.0 gm., and the white-cell count 10,000, with 83 per cent neutrophils.

In the hospital the patient continued to have some respiratory distress. A laryngoscopic examination was negative, showing normal movement of the vocal cords. A roentgenogram of the chest disclosed a large area of density in the upper mediastinal and lower cervical regions, with apparent displacement of the upper trachea and esophagus to the right. There were multiple small areas of calcification in the region of the larynx. The heart and lungs were normal. There was a marked scoliosis of the thoracic spine, with the convexity to the right. Films of the spine and pelvis were normal.

On the second hospital day while the patient was eating her evening meal respiratory distress became acute and within a few minutes she became deeply cyanotic and had a rapid, thready pulse. Efforts to pass a Mosher tube were unsuccessful. Tracheotomy was considered inadvisable because of the low position of the thyroid gland. An intratracheal tube was successfully applied by an anesthetist, and an adequate airway permitted stabilization.

A few hours later an exploration of the neck was performed.

Differential Diagnosis

Dr. Oliver Cope*: The clinical history and description of the physical examination leave no doubt that we are dealing with a large, rapidly growing tumor in the region of the thyroid gland — that is, in the lower anterior neck, displacing the trachea and, presumably, pressing on, if not displacing, the esophagus. Physical examination revealed some evidence of myxedema, and, of course, that suggests that the lesion involved and had destroyed the secreting thyroid tissue. There is evidence that the trachea was pressing upon the esophagus. Pressure without evidence of laryngeal-cord paralysis is typical of tracheal pressure; there was probably tracheal narrowing. The respiratory distress developing immediately following swallowing and the limitation of swallowing of liquids suggest, in the absence of vocal-cord paralysis, that the act of swallowing caused edema of the neck, the available space already having been taken up by the tumor; in other words, I suspect that there was a sudden rise of venous and lymphatic pressures with the act of swallowing, the edema following. It is possible that when the anesthesist put down the intratracheal tube he observed edema of the vocal cords. It will be recalled that on one day the laryngeal examination was said to be negative, and on the next day acute respiratory difficulties necessitated intubation.

The lesion that produced the obstruction is the matter for speculation. We will come to the x-ray studies in a moment in the hope that they will assist in ferreting out the origin of the mass. There are several things to consider. This mass being so rapidly growing, in a patient of the older age group, the commonest lesion is the so-called round-cell carcinoma of the thyroid gland. The patient had had an adenoacanthoma. Is it possible that this was a metastasis? I do not believe I have ever heard of an adenoacanthoma metastasizing to the thyroid gland, but I do not see why it should not. The only metastases I remember were those that might have been the result of direct extension in the abdomen, such as a metastasis to the transverse colon. I am going to dismiss adenoacanthoma because I think it is highly unlikely. Not infrequently, we find metastatic nodules in the thyroid gland from primary growths in other organs, such as the kidney, but I am going to dismiss them also for lack of evidence. The best explanation, as I have said, is the round-cell type of thyroid carcinoma. There are other tumors involving the thyroid gland that could produce this picture. I refer to the tumors developing in the neighboring organs. It is not uncommon for an esophageal tumor to invade the thyroid gland, but I do not remember one as large as this mass is described. We have seen sarcoma from the trachea on two occasions invading the gland; but, again, I do not remember a tumor as large as this, and hemorrhage had been a prominent symptom in both cases.

It is possible that this was not a carcinoma but another type of tumor of the thyroid gland. Two will have to be considered: sarcoma and lymphoma. Sarcoma may arise in the stroma or capsule of the thyroid gland, but this is a rare tumor and the patient was a little old for sarcoma. Lymphoma, although very rare, may occur as a primary lesion in the lymphoid tissue of the thyroid gland.

When one rules out tumor, there is only one lesion to be considered — that is, thyroiditis. Acute thyroiditis could cause exactly this picture: a very rapid growth in a few weeks with suffocation. I would not be surprised if Dr. Castleman told me that there was confusion regarding this specimen. Not long ago, in an elderly woman with a comparable history, the initial diagnosis of the Pathology Department was thyroiditis, and the lungs finally turned out to be sarcomatous. I believe that we might meet the same situation in this case. Rapidly growing lesions of the thyroid gland — thyroiditis, round-cell carcinoma, sarcoma and lymphoma — may be confused. Before I make my final choice, may we see the x-ray films in the hope that a primary lesion elsewhere, in the esophagus or the trachea, may give us a lead?

Dr. Stanley M. Wyman: I think the mass is quite readily visible in the lower neck and in the upper mediastinum displacing and narrowing the trachea very markedly. The esophagus is similarly displaced toward the right. I can see no evidence of intrinsic disease in the esophagus, which is displaced posteriorly as it enters the thorax. The trachea is well seen and very much narrowed, again at the opening of the thorax.

Dr. Cope: The constriction is well below the larynx.

Dr. Wyman: The lung fields appear clear. The heart shadow is prominent toward the left, and the aorta is tortuous to a degree consistent with the patient's age. The bones show osteoporosis.

Dr. Cope: The x-ray films have been helpful in showing the cause of the suffocation, and I shall have to correct a previous statement. The anesthetist may well not have seen edema of the larynx. It would not take much edema for swallowing to cut off the trachea completely. It is narrowed down to almost a slit. The act of swallowing takes up just enough more room in the upper thoracic strait to cut off the trachea. When the trachea is constricted, venous and lymphatic return are also cut off, and edema follows. With repeated swallowing the airway may be endangered by the local collection of edema at the point of tracheal narrowing. The edema may well not have extended up to the larynx itself.

Dr. Wyman does not give a clue to the origin of the tumor. One final point: it is said that no lymph

*Visiting surgeon, Massachusetts General Hospital.

nodes were palpable. On the other hand, there was a nodule the size of a lymph node at the left pole. I am not quite clear about that. Lymph-node involvement is the rule in a round-cell carcinoma of the thyroid gland. Of course, the physical examination may not have been accurate, but the absence of lymph-node involvement is presumptive evidence against a diagnosis of a round-cell type of carcinoma. If it is true that there were no lymph nodes, it is more likely that it was one of the rarer sarcomas. In thyroiditis, by the way, there are also enlarged lymph nodes commonly, and they ought to have been palpable. I do not know any way to go about it but to base it on a statistical possibility.

The first choice is a round-cell carcinoma, and I would put sarcoma or lymphoma second and thyroiditis third. I do not believe it came from the neighboring organs; I do not think it was primary in the esophagus or trachea.

Clinical Diagnosis

Carcinoma of thyroid gland.

Dr. Cope's Diagnosis

Thyroid tumor, ? round-cell carcinoma, ? sarcoma, ? lymphoma.

Anatomical Diagnosis

Fibrosarcoma of thyroid gland, with mediastinal compression and with metastases to lungs.

Pathological Discussion

Dr. Benjamin Castleman: This patient was very ill, and it was not believed that she would live after any sort of operation. It was decided to do a tracheotomy anyway, and at the same time some pieces of tumor tissue were biopsied. Everything was adherent in that region. She did poorly and died within a day of operation.

On microscopical examination of the biopsy specimen we found areas that were very fibrous and dense that looked for all the world like a Riedel struma, but in other areas there were large spindle-shaped cells, with tumor giant cells and mitoses. As Dr. Cope surmised, there was a difference of opinion in the laboratory about whether we were dealing with true Riedel's struma or very rapidly growing sarcoma. The presence of large numbers of lymphocytes and plasma cells scattered throughout the tumor spoke a bit for an inflammatory lesion, but the presence of large tumor giant cells and mitoses swayed us toward the diagnosis of fibrosarcoma. We were not completely satisfied. We thought that if it were a fibrosarcoma, it might have originated in a Riedel struma, a sequence which I had never heard of before, although we do know that in a fibrosarcoma there may be areas that are dense, fibrous and slowly growing and others that are rapidly growing.

The autopsy proved that this patient had a malignant tumor; there were several metastases in the lung measuring up to 1 cm. in diameter. Here, again, the metastases contained inflammatory cells as well, but there is no doubt that this was a malignant tumor and probably a fibrosarcoma. There are some pathologists who believe that sarcoma rarely if ever occurs in the thyroid gland and that these tumors are epithelial in nature; some are called carcinosarcomas. Some areas of the tumor were pure spindle-shaped cells, especially in the metastases. The tumor had extended into the mediastinum, compressing the neighboring structures but not invading them, which is somewhat in favor of sarcoma rather than carcinoma. An anaplastic carcinoma would tend to invade neighboring structures. This tumor pushed them aside. No regional lymph nodes were involved, which also suggests sarcoma rather than carcinoma.

Dr. Cope: I do not remember having seen a case of this type with as much fibrosis.

Dr. Castleman: Parts of the tumor were composed of such benign-looking collagen that Dr. Mallory thought that there probably was a preexisting Riedel struma.

CASE 36052

Presentation of Case

A sixty-two-year-old unmarried woman, a college dean, entered the hospital because of persistent difficulty in swallowing, which had recently become worse.

She had been seen in this hospital sixteen years previously for similar difficulty of some two years' duration. Studies at that time led to the diagnosis of "cardiospasm," and medical treatment was prescribed. During the ensuing sixteen years she had frequent bouts of difficulty in swallowing, with regurgitation of undigested food. These attacks

were almost invariably associated with episodes of emotional stress, overwork or worry and never lasted more than a few days. She was never unable to swallow liquids, never lost weight and never experienced pain, hematemesis or melena. Esophagoscopy or bouginage had never been performed. X-ray films, however, were interpreted as showing achalasia of the esophagus. During the three months before admission the symptoms became more troublesome but were unchanged in character until three weeks before entry, when she became unable to swallow anything but a small amount of liquid. She attributed her state to an exceptionally heavy load of work and worry in connection with her job.

Physical examination revealed a plump, well developed, somewhat pale, woman who seemed nervous and apprehensive. No significant abnormalities were seen; the chest was clear, the abdomen was soft and nontender without masses, and no lymph nodes could be palpated.

The temperature was 98.6°F., and the pulse 90. The blood pressure was 120 systolic, 80 diastolic.

Examination of the blood disclosed a hemoglobin of 12.6 gm. and a white-cell count of 14,000. The urine was normal except for a + test for albumin.

A chest roentgenogram showed clear lungs. The heart was normal in size, shape and position. Between the heart and thoracic spine, there was a lobulated soft-tissue mass. When this film was compared with the one taken elsewhere, it was apparent that this was a tortuous, dilated esophagus filled with food. Examination of a single anteroposterior film brought in with the patient showed a greatly dilated, barium-containing esophagus, which was tortuous in its lower third. The extreme distal portion of the esophagus appeared narrowed (Fig. 1). There was no air in the mediastinal space. The trachea was displaced upward and slightly compressed by the dilated esophagus. There was a fluid level in the esophagus opposite the second thoracic vertebra.

On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Carroll C. Miller:* With a sixteen-year story of difficulty in swallowing that had been intermittent but relatively persistent in a person of nervous temperament, who was subject to episodes of increasing emotional stress and the burden of heavy work and worry, we have a reasonably classic picture of what has been called cardiospasm or achalasia. Confirming this diagnosis are x-ray films taken previously and on this admission that showed marked dilatation of the esophagus, with a smooth, apparently concentric filling at its lower end. Incidentally, the patient's condition never deteriorated during this sixteen-year period, and she was able to maintain nutrition. The term achalasia of the esophagus refers to the absence of relaxation of the sphincter at its lower end. As much as we now know about the condition indicates that there is apparently some functional disturbance in the neuromuscular apparatus at the lower end of the esophagus, probably related to imbalance in the autonomic nervous system giving rise to abnormal function in the nerve-muscle reactions, so that over a long period the esophagus does not

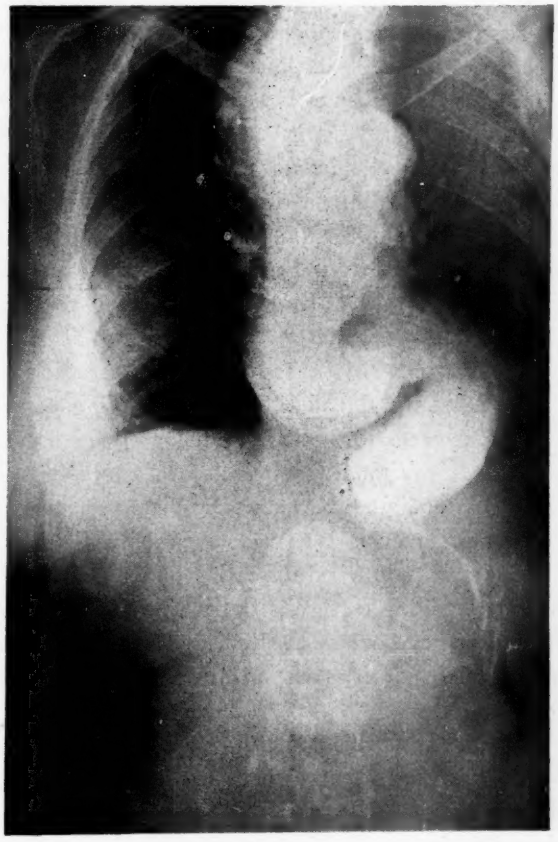

Figure 1.

*Clinical associate in surgery, Massachusetts General Hospital.

empty properly because of spasm or narrowing at its lower end. With increase in nervous tension these symptoms are exacerbated.

Before this conference I was given the privilege of examining the x-ray films taken at another hospital and the ones taken here; I will take the liberty of giving my interpretation and then asking Dr. Wyman to add what he will. The first films on the left are the two taken at the Massachusetts General Hospital, showing an irregular, rather lobulated mass in the mediastinum very clearly shown on the lateral view, with a bulge between the heart and spine. Evidently, it was not considered necessary to have additional barium studies done here. This film, taken elsewhere, shows the markedly dilated, tortuous esophagus filled with barium, down to the region of the diaphragm, where the esophagus narrows to a thin threadlike lumen and after a distance of 3 cm. enters the stomach, which can be recognized by the rugal folds in the region of the cardia (Fig. 1). Have you anything to add, Dr. Wyman?

Dr. Stanley M. Wyman: That is sufficient.

Dr. Miller: I think the most striking points about this case are the long duration of the disease and the x-ray findings, which are characteristic of what we commonly see in cardiospasm or achalasia of the esophagus. We very commonly find this tortuosity with marked dilatation of the esophagus. Another striking feature is the sharp, conical shape of the lower end, where the lumen has been narrowed without irregularity and without evidence of ulceration.

I might say at this point that in cases of this type we always suspect carcinoma in the lower end of the esophagus. We have had a number of cases giving a history of this type, in which actual carcinoma has been found superimposed on cardiospasm or stricture of the lower end. We always look for irregularity or what is described as shelf formation in the region of the constriction. I am unable to determine a definite shelf here except for a slight indentation on one side. Against carcinoma was the maintenance of weight and nutrition, and the lack of pain, which we not infrequently see in carcinoma of the esophagus from penetration of the growth posteriorly into the back, where these patients most commonly complain of pain, or from esophagitis associated with local ulceration. The blood was in reasonably good condition. She had not lost blood either by vomiting or in the stool, so that, without going into the differential diagnosis at this moment, I would favor an uncomplicated achalasia of the esophagus.

In thinking over this case I was struck by the length of the area of narrowing. It has been said that the length of the narrowing of the tube may be from 1 to 6 cm., with an average of 1 to 1.5 cm. Here it was approximately 3 cm., and I was immediately impressed by the possibility of some sort of surrounding lesion that was gradually encroaching on the whole lumen to produce this x-ray picture.

We must always think both of intrinsic lesions of the esophagus (those involving the mucosa or the esophageal wall) and of extrinsic lesions. The characteristic appearance of extrinsic lesions is simple indentation. Lymphoma, tuberculous adenitis and other tumors around the esophagus tend to produce a smooth, round, indented shadow without a concentric narrowing of the whole esophagus. The mucosal lesions, chiefly carcinoma, show ulceration in the lower end of the esophagus, which ought to be seen clearly by x-ray examination in most cases. Intramural tumors, although possibly able to produce this x-ray picture are unlikely to do so because they usually grow outward as well as inward, but the bulk of the mass is found at operation outside the esophageal wall and not surrounding the esophagus. Dr. Soutter recently had a case of leiomyoma in the upper part of the esophagus that did produce a picture similar to this. Leiomyoma is not uncommon, and it may be that in this patient a tumor enveloped the lumen of the esophagus on all sides.

The fact that she could go on for eighteen years, beginning with only intermittent difficulty in swallowing, apparently completely relieved at times, and with gradual encroachment on the lumen of the esophagus, indicates a slowly progressive type of lesion, which until very recently was not large enough to interfere completely with her deglutition.

As my final diagnosis, I repeat that I believe this patient did have probably an underlying achalasia, a narrowed area in the esophagus, with a thin wall at the site of the lesion and a thick wall of the esophagus above it. There is the remote possibility that a benign tumor of the leiomyoma or fibroma group was superimposed.

DR. EDWARD B. BENEDICT: It seems to me that Dr. Miller overemphasized the matter of pain in carcinoma of the esophagus. I do not believe we often see very much pain except in the late stages of cancer of the esophagus.

DR. MILLER: In my experience, with the onset of ulceration, many patients — not most of them to be sure — have pain as a result of obstruction and spasm of the musculature and local inflammation in the region of the lesion, but certainly the boring, persistent type of pain is found only in the penetrating tumor involving intercostal nerves.

CLINICAL DIAGNOSIS

Cardiospasm.

DR. MILLER'S DIAGNOSIS

Achalasia of esophagus.
Benign intramural tumor (leiomyoma? fibroma?).

ANATOMICAL DIAGNOSES

Squamous-cell carcinoma (Grade III) of esophagus, with lymph-node metastases.
(Cardiospasm.)

PATHOLOGICAL DISCUSSION

DR. LAMAR SOUTTER: I saw the patient preoperatively. She was a patient of Dr. Richard H. Sweet, and we were particularly impressed by the long-standing history of achalasia. We made a diagnosis of cardiospasm. At operation, a tumor mass was found involving the lower part of the esophagus, with a considerable number of local metastases necessitating resection.

DR. TRACY B. MALLORY: The specimen received in the laboratory consisted of about 12 cm. of esophagus and a segment of stomach of about equal size. The lower 6.5 cm. of esophagus was occupied by an ulcerated tumor mass grossly characteristic of carcinoma. The neoplasm had infiltrated the esophageal wall to produce two intramural tumors each about 5 cm. in diameter on either side of the cardia. These were probably chiefly responsible for the narrowing of the lumen observed by x-ray examination. Above them the esophagus was widely dilated, as is usual in cardiospasm. One metastatic lymph node, 1.5 cm. in diameter, was found in the serosa.

DR. ALLEN G. BRAILEY: How long had she had tumor?

DR. MALLORY: I do not think there is any pathological evidence to tell one beyond a matter of months. It might have been much longer.

DR. MILLER: Can Dr. Wyman give any explanation of the absence of irregular tumor defect or signs of ulceration in the x-ray films?

DR. WYMAN: I think, Dr. Miller, that we were wrong in accepting at its face value this film and not trying to demonstrate the cardia of the stomach. That ought to have given the answer. If we had proved that the gas-filled cardia, which I do not see on these films, was abnormal, we should have had a suspicion of it.

DR. MILLER: Here is another barium-enema film taken elsewhere.

DR. WYMAN: It is not helpful. At no time do we see barium entering the cardia of the stomach in the normal fashion. I think the fault lies in accepting an inadequate examination.

DR. BENEDICT: In general, I think that we should do an esophagoscopy, particularly in people of this age with a sudden change in symptoms. It should have been easily seen in an esophagoscopy.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
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MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

J' ACCUSE

THE celebrated inquisition of Dr. Miriam Van Waters, superintendent of the Reformatory for Women at Framingham, scarcely needs to be recalled, only a year later. The infamy of it struck too deeply into the minds and hearts of the majority of Massachusetts citizens to be quickly or easily forgotten.

Suffice it to say that Dr. Van Waters, who for seventeen years had proved herself a worthy successor to Clara Barton and Jessie Hodder, was on January 7, 1949, summarily removed from office by the then, and now, commissioner of correction. Twenty-seven "charges" were made against Dr. Van Waters, all of them based on technicalities, and on January 13 a "hearing" began before the commissioner and continued for eighteen days. Dr. Van Waters was herself on the stand for twelve days. After ten days more, presumably of deliberation, the commissioner sustained his own 27 charges.

Dr. Van Waters then demanded a hearing before an impartial commission and Governor Dever made an outstanding selection in the persons of Dean Erwin Griswold, of the Harvard Law School, Mrs. Roger L. Putnam, of Springfield, and Robert G. Clark, Jr., assistant district attorney of Norfolk County. This commission, having found that some of the reasons given for Dr. Van Waters's dismissal "appear to us to be trivial, and indeed captious," brought its report to a close with the following words:

> We conclude, therefore, that none of the reasons given constitutes just cause for removal. Accordingly, in the language of the statute, we "reverse the decision of the appointing authority" by unanimous action of the Commission.

Dr. Van Waters was triumphantly vindicated and returned to her post, but the same commissioner who had tried to discredit and remove her remained also in his position of authority. Worse, the same archaic statutes that keep Framingham Reformatory full of women prisoners remain on the books of Massachusetts, to the shame of the Commonwealth. These are statutes that, when interpreted by a judge who puts the letter of the law ahead of justice, may send a young woman to prison for a sentence up to five years for the theft of a loaf of bread or for having surrendered to a biologic law that is sometimes more compelling than the fear of statutory reprisal or, on the complaint of a parent, as a "stubborn child."

Light and darkness are in constant conflict. There are in Massachusetts ominous forces that still seek to stifle freedom, to subvert justice and to discredit humane motives and actions. There are in opposition to them such enlightened and determined individuals and groups as are represented by the "Friends of the Framingham Reformatory," who have been instrumental in introducing into the present session of the General Court three bills, which would modify the sentences, ameliorate the "punishments" and aid in the rehabilitation of women offenders.

House No. 358, which would amend the terms of the sentences to the Reformatory for Women

"for the crime of lewd and lascivious cohabitation and in certain cases of larceny" has already had its hearing before the Judiciary Committee. House No. 430, "an act to provide for day work outside of the Reformatory for Women for inmates of the Reformatory for Women," and House No. 431, "an act to amend the law relating to the employment of female prisoners," will be heard on February 14 before the Committee on Public Welfare.

Massachusetts, there she stands — but where?

CHLOROMYCETIN IN TYPHOID FEVER AND OTHER SALMONELLA INFECTIONS

THE results of antibiotic therapy in typhoid fever were reviewed in a recent editorial in the *Journal*.[1] The clinical results that had been reported up to that time indicated that typhoid fever was one of the few acute bacterial infections in which modern chemotherapy and antibiotics had not yielded brilliant results. A few reports on the use of aureomycin were already available at that time. They indicated that apparently favorable effects were obtained in a small proportion of the cases, but the outcome in most cases was rather equivocal. Subsequent publications have reported similar results with this agent.[2-4]

With Chloromycetin the results in the first 10 cases of typhoid fever[5] were considered highly satisfactory in that the febrile course was markedly shortened, averaging only three and five-tenths days after the treatment was begun, and clinical improvement corresponded. In spite of these apparently beneficial effects, however, the bacteriologic findings and the subsequent course in some of the patients indicated that the results of treatment with this antibiotic in typhoid fever were decidedly inferior to those usually observed with potent antimicrobial agents in many other infections — for example, with penicillin in pneumonia. Two of these first 10 patients continued to shed typhoid bacilli in their stools during convalescence; 2 others had clinical relapses with bacteremia and positive stool cultures for typhoid bacilli after the Chloromycetin was stopped and after ten to sixteen afebrile days. In addition, 1 patient had an intestinal perforation and another a massive hemorrhage from the bowel two and four days, respectively, after they had become afebrile.

Subsequent reports have given similar results.[2, 4-9] All observers have noted the beginning of clinical improvement and a drop in temperature on or soon after the third day of therapy, with rapid defervescence and symptomatic recovery after that time. However, symptomatic relapses with positive blood and stool cultures for typhoid bacilli have also been noted after cessation of therapy and after apparent recovery, and serious complications have been observed during and after Chloromycetin therapy. Persistence of the typhoid organisms in the feces during and particularly after the administration of Chloromycetin has also been observed in some patients in spite of improvement in fever and symptoms.

Smadel, Woodward and Bailey[8] have indicated that in their cases relapses occurred only in patients who received Chloromycetin for less than eight days but were not encountered in any of those who were treated with this antibiotic for more than eight days. They, therefore, advised that treatment be continued beyond that interval in order to avoid such relapses. Their experience, however, has not been duplicated by others. Thus, one of the patients treated at the Massachusetts General Hospital and reported by Collins and Finland[7] received a total of 43 gm. of Chloromycetin over a period of thirteen days and nevertheless had a very severe relapse, with positive blood and stool cultures for typhoid bacilli a week later, after being apparently well in the interim.

Schoenbach[2] also observed a patient who became asymptomatic and afebrile three days after Chloromycetin therapy but was nevertheless treated continuously for several weeks. His patient experienced a relapse two weeks after he was discharged from the hospital, and this relapse also was associated with a rash, fever and positive cultures for typhoid bacilli in the blood and stools. This patient, like all others who have been observed in similar circumstances, again responded promptly with a remission of fever and symptoms forty-eight hours after the reinstitution of Chloromycetin therapy. Treatment this time was continued for

two weeks in spite of the asymptomatic state of the patient, but this therapy failed to eliminate the typhoid organisms from his bile and stools. The patient experienced an attack of acute cholecystitis and perforation of the gall bladder twelve days after his second discharge from the hospital, and he again recovered after an operation, at which typhoid bacilli were cultured from the bile and from biliary calculi. Schoenbach suggested that the relapse rate following Chloromycetin therapy of typhoid fever is the same as that in untreated cases.

These observations and similar ones in the cases reported by Erickson elsewhere in this issue of the *Journal* indicate that Chloromycetin is a useful agent in typhoid fever and is probably the best one available at present so far as its immediate effect on the fever and symptoms is concerned. Nevertheless, it falls far short of fulfilling the real goal of modern chemotherapy, which is the complete eradication of the infecting organism. This fact is further emphasized by the failure of Chloromycetin to effect cures in chronic typhoid carriers.[7-10] Only an agent that completely eradicates the organism can be expected to ensure against relapses.

Clinical data on the effects of the newer antibiotics on salmonella infections are still scant. The report of Ross and his co-workers that also appears elsewhere in this issue is therefore of interest. These authors treated 9 cases of salmonella enteritis in infants with heavy doses of Chloromycetin and compared their results with those in 8 similar cases treated with streptomycin. Although the organisms in each case were highly sensitive to the antibiotic used, the results with both antibiotics were not very satisfactory. In only 2 of the cases treated with Chloromycetin and in 1 of those treated with streptomycin were the authors able permanently to eliminate the salmonella organisms from the stools. It is of interest that in spite of the prolonged therapy of these cases with large doses, the organisms recovered from the stools after these antibiotics were stopped retained their original sensitivity to the agents that were used. In this respect the results were similar to those observed in the treatment of typhoid fever with each of these antibiotics.

In experimental infections of mice with salmonella organisms the results of Chloromycetin therapy also have not been favorable. Seligmann and Wassermann[11] found that Chloromycetin exerts a marked inhibitory effect on the growth of salmonella organisms in vitro but is not able, even in large amounts, to control salmonella infections in mice. Neither the oral nor the subcutaneous form of treatment prevented the fatal outcome of salmonella infection in most of their animals although it prolonged their survival time.

The failure to eradicate the salmonella organisms by antibiotic agents to which they are highly sensitive in vitro is of considerable interest since this occurs in spite of the fact that adequate concentrations of these antibiotics are present during treatment in the blood and probably also in most of the body fluids. It suggests either that some of the organisms are inaccessible to the antibiotic or that they are in some way protected from the action of the antimicrobial agent. To overcome these failures either by different methods of therapy or by new and perhaps different agents poses a problem that still remains to be solved.

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INTERNATIONAL SOCIETY OF SURGERY

An event of great interest to surgeons everywhere was the thirteenth congress of the International Society of Surgery in New Orleans from October 10 to 15, with Professor George Guy Turner, of London, England, as president.

The scientific program included discussions of the following aspects of surgery, presented by in-

ternationally recognized leaders in their respective fields: "Surgery of the Parathyroids," by Professor Raffaele Paolucci, of Rome; "Surgery of the Pancreas," by Professor Ian Aird, of London; "Treatment of Postoperative Thrombosis and Its Sequelae," by Professor Alton Ochsner, of New Orleans, and Professor Michael E. DeBakey, of Houston; "Surgery of the Pituitary Gland," by Professor Paul Martin, of Brussels; "Surgery of the Suprarenal Glands," by Professor Rene Fontaine, of Strasbourg; and "Causes of Recurrences after Operation on the Biliary Tract," by Professor Rudolf Demel, of Vienna. The meeting of the American Branch of the Society on the two final days of the congress consisted of lectures on subjects of equal timeliness and importance, and the value of the congress was still further enhanced by the clinical program at the famous Charity Hospital of New Orleans and operative clinics in other hospitals in the city.

Over a period of nearly forty-five years, congresses of the International Society of Surgery have been held in Brussels, Paris, London, Rome, Warsaw, Madrid, Cairo and New York City. The choice of New Orleans as the site of the second congress in the United States was felicitously commemorated by the selection, as honorary chairman, of the former president of the Society, Dr. Rudolf Matas, whose name is intimately associated not only with the delightful city in which he resides but also with the practice of surgery in both hemispheres.

POWER OF THE PEN

THE Government Printing Office, according to *National Economic Council Letter* of November 15, 1949, reprinted by Massachusetts Hospital Service Inc., has estimated that between 1939 and 1949 nearly 13,400,000 copies of publications were printed each year for public distribution. The ten-year total can easily be obtained by adding a zero to the tail of this astronomical figure.

Much of this material having been distributed in the interests of public information and education, a glance at a few of the titles may be of interest. These include such subjects as "How to Tell the Sex of a Watermelon," "Techniques of Fishpond Management," "Estimating Muskrat Population by House Count," "Fish for Breakfast — and Why Not?", "Fairy Tales from Korea," "Recipes for Cooking Muskrat Meat," "Mist Netting for Birds in Japan," "Habits, Food, and Economic Status of the Band-Tailed Pigeon," and "A New Name for the Japanese Blue Magpie."

The education of the American people must have breadth as well as depth.

The London College of Physicians and Surgeons have decided, that, for the future, the candidates for their fellowship shall pass an examination in Greek, Latin, mathematics and French!

Boston M. & S. J., *January 30, 1850*

MASSACHUSETTS MEDICAL SOCIETY

BILLS FOR ANNUAL DUES

A number of fellows of the Society appear to have misconstrued the wording of the bill for annual dues that they received last month.

According to the vote of the Council passed on February 5, 1947, the dues of the Society were raised to $25 as of January 1, 1948. Of each $25 thus received $5 was allocated to the support of the Boston Medical Library, and each fellow of the Society became thereby a member of the Library, with the usual privileges, including that of having books sent to him on the payment of transportation charges only.

The sum of money that the Library receives from these dues pays part, but by no means all, of its necessary expenses.

H. QUIMBY GALLUPE, *Secretary*

SHATTUCK LECTURE

Dr. Merrill C. Sosman, roentgenologist of the Peter Bent Brigham Hospital, has been selected by the Committee on Publications to deliver the Shattuck Lecture at the annual meeting of the Society in May.

His subject will be "Specificity and Reliability of Roentgen Diagnosis."

DEATHS

FAWCETT — Deborah Fawcett, M.D., of Newton, died on December 31. She was in her eightieth year.

Dr. Fawcett received her degree from Boston University School of Medicine in 1903.

A brother, a sister and two nephews survive.

HOWES — Frank M. Howes, M.D., of New Bedford, died on December 22. He was in his sixty-fifth year.

Dr. Howes received his degree from Harvard Medical School in 1910. He was president of the medical staff of St. Luke's Hospital, a member of the New England Heart Association and a fellow of the American Medical Association.

Two daughters, five grandchildren and a sister survive.

McDERMOTT — William V. McDermott, M.D., of Salem, died on January 16. He was in his seventy-seventh year.

Dr. McDermott received his degree from Harvard Medical School in 1896. He was formerly chairman of the Salem Board of Health, chief of the Neurological Service at Carney Hospital and assistant in neurology at Massachusetts General Hospital and was a fellow of the American Medical Association.

His widow, a son, two grandchildren and a sister survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1949

RÉSUMÉ

DISEASES	DECEMBER 1949	DECEMBER 1948	SEVEN-YEAR MEDIAN
Chancroid	0	3	3*
Chicken pox	1455	3024	1444
Diphtheria	18	47	32
Dog bite	666	654	517
Dysentery, bacillary	13	2	12
German measles	38	83	72
Gonorrhea	186	257	316
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	1	1*
Malaria	1	0	7
Measles	113	4674	840
Meningitis, meningococcal	6	7	12
Meningitis, Pfeiffer bacillus	7	5	5
Meningitis, pneumococcal	4	7	7
Meningitis, staphylococcal	0	1	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	5	7	3
Mumps	567	1319	1080
Poliomyelitis	18	2	11
Salmonellosis	3	4	5
Scarlet fever	268	698	698
Syphilis	109	180	373
Tuberculosis, pulmonary	227	216	207
Tuberculosis, other forms	12	15	13
Typhoid fever	0	2	3
Undulant fever	0	1	3
Whooping cough	448	331	598

*Five-year median.

COMMENT

The only diseases significantly above the seven-year median were dog bite and poliomyelitis. Compared with the 724 cases in August and 603 cases in September, the incidence of 18 cases of poliomyelitis in December does not seem high.

Diseases below the seven-year median included diphtheria, German measles, measles, mumps, scarlet fever and whooping cough.

Measles was at the lowest level ever recorded for December, with only 113 cases, compared to a seven-year median of 840 cases. Scarlet fever was also at the lowest point ever recorded in December. This was the sixth month that scarlet fever remained at the lowest level ever recorded.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Belchertown, 1; Boston, 10, Brookline, 1; Cambridge, 1; Groton, 1; Halifax, 1; Lynn, 2; Wilmington, 1; total, 18.

Dysentery, bacillary, was reported from: Boston, 7; Worcester, 6; total, 13.

Encephalitis, infectious, was reported from: New Bedford, 1; Newton, 1; total, 2.

Malaria was reported from: Peabody, 1; total, 1.

Meningitis, meningococcal, was reported from: Boston, 1; Brockton, 1; Fall River, 1; Newton, 2; Quincy, 1; total, 6.

Meningitis, Pfeiffer-bacillus, was reported from: Belmont, 1; Cambridge, 1; Gloucester, 1; Lowell, 1; Worcester, 3; total, 7.

Meningitis, pneumococcal, was reported from: Cambridge, 1; Chelsea, 1; Lowell, 1; Salem, 1; total, 4.

Meningitis, undetermined, was reported from: Boston, 1; Chelmsford, 1; Fall River, 2; Plainville, 1; total, 5.

Poliomyelitis was reported from: Attleboro, 1; Boston, 1; Bridgewater, 1; Canton, 1; Carlisle, 1; Fall River, 1; Falmouth, 1; Fitchburg, 1; Hingham, 1; Lynn, 1; Newburyport, 1; Orange, 1; Quincy, 1; Revere, 1; Saugus, 1; Shrewsbury, 1; Tyngsboro, 1; Weymouth, 1; total, 18.

Salmonellosis was reported from: Everett, 1; Salem, 1; Somerville, 1; total, 3.

Septic sore throat was reported from: Adams, 1; Boston, 4; Braintree, 1; total, 6.

Trachoma was reported from: Whitman, 1; total, 1.

Trichinosis was reported from: Boston, 2; Cambridge, 1; total, 3.

MISCELLANY

AMERICAN HEART ASSOCIATION AWARDS

The American Heart Association has named 34 investigators among whom $140,000 in awards for research will be divided.

Included among these, in the New England area, are: Dr. John P. Merrill, working on further developments of the artificial kidney at the Peter Bent Brigham Hospital; Robert E. Olson and Isidore S. Edelman, working in biochemistry at Harvard Medical School; and John H. Heller, working on hypertension, at Yale University.

CORRESPONDENCE

DEPRIVATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held January 12, it was voted to suspend the registration of Dr. Kenneth J. Tillotson, of Belmont, for three months followed by nine months' probation.

GEORGE L. SCHADT, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

IN FAVOR OF PILOT CLINIC

To the Editor: A few members of the Society have voiced opposition to the action of the Council in authorizing the establishment of a multiphasic pilot clinic for the free examination of the apparently well. It was the hope of the Committee on Public Health in recommending these clinics to the Council that they would develop a pattern to take the place of the various drives for the discovery of hidden evidence of disease in one system only.

The object in establishing these clinics was to crystallize some of the recommendations brought out at the Massachusetts Health Conference held in February, 1949. The Conference itself was suggested by officers of the Society. It was intended to demonstrate to the people at large that organized medicine was making an effort to solve the health problems of the public. I believe that this is good public relations.

The opposition referred to was based on the assumption that the clinic would take away work from the office of the physician and that it would advance state medicine.

The first criticism has frequently been encountered in attempts to popularize new procedures in preventive medicine. That this is a wrong assumption has been amply proved, and a precedence for such activities is provided by the following statement of the Committee on Public Health in the report for the year ending May 31, 1921:

> In view of demonstrated practical value of the Schick test and . . . the immunization with toxin-antitoxin against diphtheria, the committee has undertaken to give to the physicians in various parts of the State an opportunity to gain personal instruction in making the test, interpreting the reaction and giving the toxin-antitoxin mixture.

The Committee engaged a recent graduate, Dr. Joseph Garland, now the editor of the *Journal*, to carry on this work in various parts of the State. A large part of the expenses

of the Committee for the years ending May, 1921, and May, 1922, consisting of $1200, was devoted to this project.

Part of Dr. Garland's work was done in Worcester, and I remember with some satisfaction that I was among the first to be given a Schick test and immunized at that time. After this demonstration the Board of Health took up the work and carried it on in spite of some opposition on the grounds that it was taking away one of the practicing physicians' means of livelihood. However, the efficacy of this procedure made it so popular that people demanded it from their family physician, and today the Department of Public Health is doing less and less and the family physician more and more.

The second criticism — that the clinic will advance state medicine — to my mind is a fallacy; I am confident that in various ways, this being one of them, physicians can prove that free medicine can do a better job than state-controlled medicine.

It is my belief that this pilot clinic will develop a method for searching out the early beginning of disease, which the physician can follow, and that it will become so popular that it will lead many patients into the doctors' offices for this preventive work.

ROY J. WARD, M.D.

Worcester, Massachusetts

BOOK REVIEWS

Mobilization of the Human Body: Newer concepts in body mechanics. By Harvey E. Billig, Jr., M.D., F.I.C.S., and Evelyn Loewendahl, M.A., Ph.T. 8°, cloth, 65 pp., with 25 illustrations. Stanford, California: Stanford University Press, 1949. $2.00.

This booklet of 62 pages contains a thought-provoking discussion of the problem of stiffness. Stiffness from many causes is often found in youth but is an almost universal finding after middle age. The booklet is written for the lay reader rather than the physician. The authors approach the posture problem from the point of view of mobility rather than alignment. They state truly that ability to balance is impossible if movement is restricted. Whether specific stretching for a specific area of the body should precede or follow general postural exercises is still a moot question. There is no doubt that the procedures here described are of value in recovery of function. There are many good illustrations. There is no bibliography.

The Development of Gynaecological Surgery and Instruments: A comprehensive review of the evolution of surgery and surgical instruments for the treatment of female diseases from the Hippocratic age to the antiseptic period. By James V. Ricci, M.D. 4°, cloth, 594 pp., with illustrations. Philadelphia: Blakiston Company, 1949. $12.00.

The distinguished gynecologist who is the author of this unique and delightful monograph has no occasion to apologize, as he does, for temporarily forsaking the clinical field and "invading the province of the medical historian" to present the historical background of gynecologic surgery and instruments and to assemble systematically the surgical innovations in this specialty from the Hippocratic dawn to the antiseptic age. The knowledge of medical history would benefit immeasurably if other clinicians would follow his admirable example.

After a brief introductory chapter on Graeco-Roman gynecologic instruments, the author describes and figures in detail those mentioned in the Hippocratic collection, those found at Pompeii, those recorded in the Byzantine medical compilations and the Arabian medical texts. At even greater length are described the gynecologic surgery and instruments of the Middle Ages and of the Renaissance. Finally, and in the fullest detail, are considered those of the seventeenth, the eighteenth and the nineteenth centuries.

The entire volume is amply provided with an abundance of 220 well chosen illustrations, and has a total of 1647 selected references to the literature, often with suitable and illuminating quotations. This is a work of thorough and competent scholarship, as well as of expert modern clinical acumen. It is a very valuable contribution to the history of gynecology.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Pathology of the Nervous System: A student's introduction. By J. Henry Biggart, C.B.E., M.D., D.Sc., professor of pathology, Queen's University, Belfast, pathologist to the Royal Victoria Hospital, Belfast Hospital for Sick Children, Claremont Street Hospital for Nervous Diseases and Mater Infirmorum Hospital. With a foreword by Professor A. Murray Drennan, M.D., F.R.C.P.E., F.R.S.E. Second edition. 8°, cloth, 352 pp., with 232 illustrations and 10 colored plates. Baltimore: Williams and Wilkins Company, 1949. $6.00.

This manual for students has been revised, and some chapters have been largely rewritten. A number of new half-tone and colored illustrations have been added. Lists of selected references are appended to the various chapters, but no attempt has been made to convert the book into a reference work. The type, printing and illustrations are excellent, and there is a good index. The printing was done in Great Britain.

A Manual of the Penicillia. By Kenneth B. Raper, principal microbiologist, Fermentation Division, Northern Regional Research Laboratory, Bureau of Agricultural and Industrial Chemistry, United States Department of Agriculture, Peoria, Illinois; and Charles Thom, collaborator, United States Department of Agriculture. With the technical assistance and illustrations by Dorothy I. Fennel, assistant microbiologist, National Science Fund and Cooperative Agent, United States Department of Agriculture, Peoria, Illinois. 8°, cloth, 875 pp., with 172 illustrations. Baltimore: Williams and Wilkins Company, 1949, $12.00.

Penicillium, the generic name of a group of green molds, has been known for a hundred and forty years. The penicillia now assume great importance because of the discovery of penicillin by Alexander Fleming, in 1928, and its subsequent, wide use in the treatment of infections. This work is designed primarily for the identification of penicillin in the laboratory, or for any reason that may be significant in microbiology or biochemistry. The text is divided into three main parts; general; the manual of recognized species of penicillium; and reference material. The first part comprises a short history of penicillium, the generic diagnosis, synonymy, observation, description, cultivation and preservation of penicillia and a short chapter on penicillin. The second part, the manual proper, describes the individual species and presents the available information concerning their physiology, biochemistry and pathogenicity. The third part includes extensive topical and general bibliographies, a species index and a list of accepted species and varieties. There is a good index, and the publishing is excellent. The book is recommended for all medical, scientific and general libraries. It should become the standard reference work on the subject.

Mental Hygiene in Public Health. By Paul V. Lemkau, M.D., associate professor of public-health administration and director, Mental Hygiene Study, Johns Hopkins University School of Hygiene and Public Health. 8°, cloth, 396 pp., with 8 illustrations. New York: McGraw-Hill Book Company, Incorporated, 1949. $4.50.

This volume forms one of the *McGraw-Hill Series in Health Science.* The book is the product of many minds, the ideas and facts being drawn from too many sources to be acknowledged. The material is divided into two parts: the place of mental health in public health, in five chapters; and the development of the individual, in ten chapters. In the second part the author traces the development of the personality from the prenatal period through old age. A number of case histories are interspersed throughout the text. The material is based on a course on mental hygiene given in the School of Public Health of Johns Hopkins University. Two appendixes present a review of the psychopathologic states, and a list of visual aids arranged by age periods. It is hoped that the material will provide an effective basis for the organization of con-

structive programs for the promotion and the protection of the mental health of the population. The text is well printed with a good type. The use of a heavy, coated paper, making the volume too heavy for its size, is not justified for the type of book. Lists of references are appended to the various chapters. There are separate indexes of authors and subjects. The book should be in all medical libraries and should prove valuable to pediatricians, psychiatrists and educators.

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The following is the schedule of meetings of the Boston City Hospital House Officers' Association for February:

Dr. Selman Waksman, director of the Microbiological Institute, Rutgers University, will speak on the subject "Antibiotics, or a Search for Chemotherapeutic Agents." The discussers will be Drs. Chester S. Keefer and Maxwell Finland. The meeting will be held at 7 p.m. on Tuesday, February 7, in the Dowling Amphitheater.

The Harvard Medical Society meeting will be held on Tuesday evening, February 14, in place of the regular Tuesday evening meeting. The chairman will be Dr. Raymond Adams.

DELTA OMEGA LECTURE

Dr. William P. Shepard, of San Francisco, third vice-president of the Metropolitan Life Insurance Company and president-elect of the American Public Health Association, will deliver the Delta Omega Lecture in the amphitheater of Building B, Harvard Medical School, on Monday, February 13, at 4 p.m. His subject will be "The Training and Recruitment of Professional Public Health Personnel."

The Delta Omega Lecture is sponsored by the Beta Chapter of Delta Omega, the Harvard School of Public Health Chapter of the national honorary scholastic society in public health.

Persons interested in training and education of public-health workers are cordially invited to attend.

NEW ENGLAND CONFERENCES ON ALLERGY AND RELATED SUBJECTS

The New England Conferences on Allergy and Related Subjects will be held on Wednesday afternoon and evening, February 15. The afternoon program, consisting of the presentation of cases of bronchial asthma and illustrating the use of special technics in diagnosis and the use of Cortisone in treatment, will be held in the amphitheater of the Evans Memorial Hospital, 65 East Newton Street, Boston, from 3:30 p.m. to 5:30 p.m.

At the evening program, which will take place in the State Suite of the Copley Plaza Hotel, Boston, at 8:30 p.m., Dr. Bram Rose, of McGill University Faculty of Medicine and the Royal Victoria Hospital, Montreal, will discuss "The Effect of ACTH on Bronchial Asthma and Other Conditions of Hypersensitivity."

A dinner at the Copley Plaza Hotel, Boston, for the convenience of those attending the program will take place at 7:00 p.m. Reservations may be made on or before February 10 by application to Dr. Irving W. Schiller, 65 East Newton Street, Boston 18, Massachusetts, enclosing a check for $4.50 to cover the expenses of the dinner.

All members of the medical profession are cordially invited to both the afternoon and evening meetings.

SPRINGFIELD HOSPITAL

The following is the educational program of the Springfield Hospital for the next month:

Saturday, February 18. 11:00 a.m. Springfield Hospital's Guest Speaker Conference in the Staff Conference Room. Dr. Ernest M. Daland will speak on the subject "Malignant Melanomas."

Tuesday, February 21. 8:30 p.m. Clinicopathological conference in the Staff Conference Room.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3–MAY 19. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

FEBRUARY 6. New England Cardiovascular Society. Page 160, issue of January 26.

FEBRUARY 6. Hartford Medical Society. Page 160, issue of January 26.

FEBRUARY 7. Boston City Hospital House Officers' Association. Notice above.

FEBRUARY 9. Lobotomy and Its Uses. Dr. Storer P. Humphreys. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

FEBRUARY 9. Alpha Omega Alpha Lecture. Page 160, issue of January 26.

FEBRUARY 13. Delta Omega Lecture. Notice above.

FEBRUARY 14. New England Society of Anesthesiologists. Page 76, issue of January 12.

FEBRUARY 14. Harvard Medical Society. See Boston City Hospital House Officers' Association. Notice above.

FEBRUARY 15. New England Conferences on Allergy and Related Subjects. Notice above.

FEBRUARY 18. Springfield Hospital. Notice above.

FEBRUARY 20. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.

FEBRUARY 20. Hartford Medical Society. Page 160, issue of January 26.

FEBRUARY 20–23. American Academy of General Practice. Page 252, issue of August 11.

FEBRUARY 21. Springfield Hospital. Notice above.

APRIL 17. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.

APRIL 24–28. National Tuberculosis Association. Page 678, issue of October 27.

APRIL 26. New England Obstetrical and Gynecological Society. Rhode Island Hospital and Providence Lying-in Hospital, Providence, Rhode Island.

MAY 3. Norfolk District Medical Society Anniversary Dinner.

MAY 14–19. International and Fourth American Congress on Obstetrics and Gynecology. Page 160, issue of January 26.

MAY 16–18. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

JUNE 24 AND 25. American Society for the Study of Sterility. Page 38, issue of January 5.

JULY 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

(*Notices concluded on page xix*)

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8

NOTICES (*Concluded from page 196*)

SEPTEMBER 3-9. International Heart Congress. Page 160, issue of January 26.

SEPTEMBER 27-29. Mississippi Valley Medical Society. Page 991, issue of December 15.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

DISTRICT MEDICAL SOCIETY

NORFOLK

FEBRUARY 28.
MARCH 28.
MAY 3. Anniversary Dinner.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 9

FRIDAY, FEBRUARY 10

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

MONDAY, FEBRUARY 13

*11:30 a.m.–12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*4:00 p.m. Delta Omega Lecture. Amphitheater of Building B, Harvard Medical School.

TUESDAY, FEBRUARY 14

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, FEBRUARY 15

*11:00 a.m.–12:00 m. Medical Rounds. Children's Medical Center.
*12:00 m. X-Ray Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic of all Medical Center Services. Amphitheater, Children's Hospital.
*3:30 p.m. New England Conferences on Allergy and Related Subjects. Evans Memorial Hospital and Copley Plaza Hotel, Boston.

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